UNIVERSITY OF ALBERTA

The Effects of Helium-Oxygen on Exercise Tolerance and Cardiopulmonary Function.

by

Neil Derek Eves ©

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of the requirements for the degree of Doctor of Philosophy

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Dedication

To Mum and Dad
I could not wish for better parents.

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ABBREVIATIONS

Bla^-	blood lactate
BTPS	body temperature and pressure saturated
CO_2	carbon dioxide
CON	control trial
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
DH	dynamic hyperinflation
D_{LCO}	diffusion capacity of the lung for carbon monoxide
EDCA	end diastolic cavity area
EELV	end expiratory lung volume
EFL	expiratory flow limitation
EILV	end inspiratory lung volume
ESCA	end systolic cavity area
ESMA	end systolic myocardial area
ESTA	end systolic total cavity area
f	breathing frequency
FAC	fractional area change
FEV_1	forced expired volume in one second
F_IO_2	fraction of inspired oxygen
FRC	functional residual capacity
FVC	forced vital capacity
GXT	graded exercise trial
HCO_3	bicarbonate
Hb	hemoglobin
Hct	hematocrit.
He	helium
HE-OX	normoxic-helium (21%O2, 79%He)
HE-HOX	hyperoxic-helium (40%O2, 60%He)
HOX	hyperoxia (40%O2, 60%N2)
HR	heart rate
IC	inspiratory capacity
IRV	inspiratory reserve volume
IT1	isotime one
IT2	isotime two
IT3	isotime three
LV	left ventricle
LVEDV	left ventricular end diastolic volume
LVESV	left ventricular end systolic volume
MEP	maximal expiratory mouth pressure
MIP	maximal inspiratory mouth pressure
MVV	maximal voluntary ventilation
N_2	nitrogen
O_2	oxygen
PACK	air cylinder and harness assembly only trial

P_aCO_2	partial pressure of arterial carbon dioxide
P_aO_2	partial pressure of arterial oxygen
P_E	expiratory mouth pressure
$PEEP_i$	intrinsic positive end expiratory pressure
P_I	inspiratory mouth pressure
P_{pa}	pulmonary artery pressure
PO	power output
PRD	perceived respiratory distress
PVR	pulmonary vascular resistance
REG	regulator only trial
RER	respiratory exchange ratio
RPE	ratings of perceived exertion
RV	right ventricle
SA	stroke area
SCBA	self –contained breathing apparatus
S_aO_2	arterial saturation
S_pO_2	oxyhemoglobin saturation measured with pulse oximetry
S_{Raw}	specific airway resistance
SV	stroke volume
T_E	expiratory time
T_I	inspiratory time
T_I/T_{TOT}	duty cycle
T_{TOT}	total time of one ventilatory title
TLC	total lung capacity
V_E	ventilation
V_E/VCO_2	ventilatory equivalent for carbon dioxide
V_E/VO_2	ventilatory equivalent for oxygen
VCO_2	carbon dioxide produced
VO_2	oxygen consumption
VO_{2max}	maximal oxygen consumption
VO_{2peak}	peak oxygen consumption
V_T	tidal volume
VT	ventilatory threshold
V_T/T_E	expiratory flow
W_{IP}	inspiratory elastic work to overcome PEEPi
W_{INP}	inspiratory elastic work to overcome the non-PEEPi elastic load

CHAPTER I

General Introduction

This introduction will highlight the pertinent literature that facilitated the development of the research studies in this thesis. Due to the nature of the three separate investigations performed, the introduction will also consist of three separate, but not mutually exclusive parts. The first section will discuss how the external expiratory resistance of the self-contained breathing apparatus (SCBA) may adversely affect exercise tolerance by imposing a mechanical constraint to ventilation (V_E). Secondly, the potential benefits of breathing helium-based and/or hyperoxic gas mixtures for reducing the ventilatory constraint with the SCBA will be addressed. The concluding section will then discuss how these gas mixtures could also be beneficial for improving cardiopulmonary interaction and exercise tolerance in patients with chronic obstructive pulmonary disease (COPD).

Self Contained Breathing Apparatus and Exercise

Firefighting involves physically strenuous work that places considerable demands on the energy systems of the body. In combination with the highly physical nature of the occupation, firefighters are frequently placed under additional stress by the environment and their personal protective equipment. Inside a burning structure, the ambient temperature can rise above 232°C (Abeles et al., 1973) and the air can be filled with ash, smoke and a variety of other pollutants. To protect the firefighter from these conditions, protective clothing and a self-contained breathing apparatus must be worn. Few studies have ever investigated the effects of either the protective clothing or the SCBA on exercise tolerance, but those that have consistently report an attenuation of work capacity (Raven et al., 1977; Louhevaara et al. 1985, 1986; White, 1989) and elevated physiological responses to exercise at submaximal work rates (Romet and Frim, 1987; Baker et al., 2000).

To date, it is unknown whether the expiratory resistance of the modern SCBA regulator increases breathing resistance to a level that impedes maximal expiratory flow rates. However, if this is the case, then it is feasible that the expiratory breathing resistance imposed by the SCBA could reduce V_E, increase respiratory muscle work, and attenuate maximal oxygen consumption (VO_{2max}). Furthermore, if the SCBA does impose an expiratory flow limitation (EFL) and constrain V_E, then an intervention that could reduce breathing resistance may have significant implications for improving exercise capacity.

Previous studies with demand style regulators (Louhevaara et al., 1984) have demonstrated that during heavy work, V_E and tidal volume are greatly reduced. Louhevaara and colleagues (1985) also postulated that the weight of the SCBA cylinder and the shoulder straps of the harness assembly might hinder chest wall mechanics in a way that mimics a restrictive ventilatory impairment. However, unlike the SCBA used by Louhevaara et al., (1984), modern SCBA maintain a positive pressure within the face piece, which provides inspiratory assistance even at maximal exercise. Furthermore, even though the heavier steel cylinders are still used by some fire departments, the cylinder harness has been improved for better comfort and weight distribution. It therefore remains unknown whether the present day SCBA will also have the same effect to that observed by Louhevaara and colleagues.

The effects of the SCBA on maximal oxygen consumption has also not been studied, likely due to the difficulties in collecting expired gases while wearing the SCBA. In an earlier study, we designed a plexiglass cone that provided an airtight seal over the exhalation ports of the SCBA regulator (Eves et al., 2002a). This device allowed collection of expired gases and accurate assessment of VO_{2max} while wearing the SCBA regulator. However, this study was designed to investigate the effects of breathing hyperoxia on maximal and submaximal exercise performance with the SCBA, so the effects of the SCBA on VO_{2max} are still unknown. A number of important questions, therefore, still remain unanswered. Firstly, does the SCBA attenuate V_E and VO_{2max}? Secondly, if the SCBA does reduce VO_{2max}, to what extent does each individual component (e.g. breathing regulator or cylinder and harness assembly) contribute to the ventilatory constraints and reduced maximal exercise performance observed?

The Effects of Helium and Hyperoxia on Exercise Performance with the SCBA

It is now commonly accepted that hyperoxia decreases V_E during submaximal exercise (Byrnes and Mullin 1981) and can improve maximal oxygen consumption in athletes (Knight et al. 1993; Nielson et al. 1998). Studies performed with the SCBA have also demonstrated that hyperoxia decreases the recovery time needed between bouts of high intensity intermittent work (van den Berg et al., 1977) and can decrease the time needed to perform simulated firefighting tasks (Petersen et al., 2000). Previous research conducted by the author has also demonstrated that hyperoxia can improve VO_{2max} and peak power output during a graded exercise test to exhaustion (Eves et al., 2002a). Furthermore, during 20 minutes of sustained exercise at the anaerobic threshold, hyperoxia reduced V_E, expiratory mouth pressure, heart rate, blood lactate concentration and the symptoms of perceived exertion and perceived breathing distress with the SCBA (Eves et al., 2002b).

The findings from these two studies (Eves et al., 2002a,b) also gave insight into the mechanisms responsible for the improved exercise performance with hyperoxia. Firstly, during the maximal exercise tests, hyperoxia prevented oxyhemoglobin desaturation, which increased O_2 delivery and augmented O_2 extraction (C_aO_2-C_vO_2). It was estimated that the improvement in C_aO2-C_vO_2 explained 97% of the increase in VO_{2max} (Eves et al., 2002a). The reduced ventilatory demand with hyperoxia also reduced expiratory flow rates and decreased ventilatory effort during work at the anaerobic threshold. This reduced ventilatory effort with hyperoxia, combined with an attenuated blood lactate response, likely explain the improved ratings of perceived exertion and breathing distress observed with this gas. While exercise limitation was not compared between hyperoxia and compressed air, it is safe to assume that the reduced ventilatory effort, blood lactate and exertional symptoms with hyperoxia would translate into an improved exercise tolerance.

While VO_{2max} was increased with hyperoxia in our previous study (Eves et al., 2002a), it was also notable that at exhaustion in the hyperoxia trials V_E, expiratory mouth pressures and exertional symptoms were similar to those obtained while breathing compressed air. These findings demonstrate that the ventilatory constraints caused by the SCBA are delayed, but not reduced with hyperoxia. In contrast, normoxic-helium mixtures have been shown to improve expiratory flow limitation and increase V_E in athletes (Buono and Maly, 1996) and individuals with expiratory flow limitation (Richardson et al., 1999; Babb et al., 2001).

Similar to nitrogen (N_2), helium (He) is a non-toxic, inert gas that is nonreactive with biological membranes and is almost insoluble in tissues (Jaber et al., 2001). However, the density of normoxic-helium (HE-OX), is approximately three times lower than the density of air and combined with a relatively small increase in dynamic viscosity (8%), results in a reduction in turbulent flow. As the SCBA regulator has a greater diameter than even the largest respiratory airways, it is likely to produce considerably greater turbulence to airflow than mouth breathing. Therefore, a helium-based gas could be beneficial for improving EFL and enhancing V_E at maximal exercise with the SCBA. Furthermore, at submaximal levels the resistive unloading of the SCBA regulator with helium could have implications for reducing the external expiratory breathing resistance and decreasing the effort needed to produce a given V_E.

At present, no known investigation has studied the effect of combining helium and hyperoxia on exercise capacity with the SCBA and only one study has previously investigated the effects of helium-hyperoxia on exercise performance during mouth breathing (Wilson and Welch, 1980). In this study, the authors demonstrated that compared to room air, normoxic-helium (20% O_2, 80% He) and hyperoxia (80% O_2, 20% N_2) increased exercise time to exhaustion in normal individuals by 8.4% and 21.8%, respectively. However, the increase in time to exhaustion with a helium-hyperoxic gas (80% O_2, 20% He) was of a greater magnitude than the other two gas mixtures combined (35.7%). As the SCBA imposes a greater expiratory resistance to breathing, a helium-hyperoxia mixture could combine the effects of both the normoxic-helium and the hyperoxic gas and restore exercise capacity to level similar to mouth breathing.

Dynamic Hyperinflation and Dyspnea in COPD

Similar to the proposed ventilatory limitations with the SCBA, the pathophysiological EFL inherent to COPD patients can also have a negative affect on exercise tolerance. In individuals with normal pulmonary function, end-expiratory lung volume (EELV) corresponds closely with the elastic equilibrium volume, or relaxation volume of the respiratory system (Ninane 1997). At the initiation of exercise, the increase in V_E is primarily a function of enhanced tidal volume, achieved by decreasing EELV and increasing end inspiratory lung volume (EILV). The ability to reduce EELV below relaxation volume with exercise maintains EILV at a lower percentage of total lung capacity (TLC) and minimizes the elastic work of breathing associated with elevated lung volumes (Road et al., 1986). In contrast, COPD patients have an impaired ability to empty the lungs due to increased airway resistance and reduced elastic lung recoil. As a consequence, expiratory time may not be sufficient to allow EELV to reach relaxation volume before the next inspiration is initiated (Ninane et al., 1993). This increase in EELV above relaxation volume is referred to as dynamic hyperinflation (DH) and occurs in an attempt to enhance expiratory flow rates and prevent dynamic airway closure during expiration (Somfay et al., 2001).

As a result of DH, EILV also increases in an attempt to maintain tidal volume. When EILV approaches TLC, the inspiratory reserve volume (IRV) is greatly reduced and any additional increase in V_E must come from an increase in respiratory rate.

However, an elevation in breathing frequency only exacerbates the problem and the extent of DH increases due to the further reductions in expiratory time (O'Donnell et al., 1997a). At lung volumes close to TLC, tidal breathing is moved to the flatter portion of the pressure-volume curve, lung compliance is decreased and a greater elastic load is placed on the muscles of inspiration (Yan et al., 1997a). In addition, the hyperinflation flattens the diaphragm and shortens all inspiratory muscles reducing their force generating capacity (LeBlanc et al., 1988; Sinderby et al. 2001). Therefore, DH markedly increases the elastic work of breathing and elevates inspiratory muscle demand, while concomitantly decreasing the capacity of the respiratory muscles to generate pressure. Another consequence of DH is that alveolar pressure remains positive when expiratory flow ceases (Sharp, 1983; Aldrich et al., 1993). This systematic consequence of DH is termed intrinsic positive end expiratory pressure (PEEPi) and adds an inspiratory threshold load to inspiration that has to be overcome before inspiratory flow can start (Dal Vecchio et al., 1990).

Due to the heterogenic nature of COPD, the mechanisms responsible for dyspnea vary between individuals. However, dyspnea is believed to arise from a mismatch between neural activity and the consequent mechanical or ventilatory afferent signals produced by the respiratory system (Schwartzstein et al., 1989; Banzett et al., 1990). The inequality between respiratory drive and sense of respiratory effort is evident during physical exertion in patients with COPD and appears to be related to the extent of DH that occurs with exercise (O'Donnell et al., 1997a).

As a consequence of DH the muscles of inspiration work at a greater percentage of their maximal capacity during exercise, which has been shown to be a major contributor to exertional dyspnea (Killian and Jones, 1988; O'Donnell et al., 1997a). Furthermore, O'Donnell et al., (1997b) reported a strong correlation between perceived inspiratory effort and the ratio of ventilatory effort and ventilatory output. These findings suggest that perceived inspiratory difficulty is not only a function of the magnitude of inspiratory muscle contractile effort but is also modulated by feedback that may provide information about the "appropriateness" of the ventilatory response for any given effort (O'Donnell et al., 1997a).

Further evidence for the role of dynamic hyperinflation and increased respiratory muscle work being major contributors to exertional breathlessness in COPD comes from studies that have reduced operational lung volumes and/or inspiratory muscle effort and found improvements in dyspnea. O'Donnell et al., (2001b) decreased DH by reducing ventilatory demand and breathing frequency with hyperoxia, in 11 severe COPD patients. Reductions in DH correlated with dyspnea rating and were associated with improved exercise tolerance. Similarly, Belman et al., (1996) demonstrated that reduced DH after an inhaled beta agonist was the best predictor of reduced breathlessness during a symptom limited exercise test. Finally, in a different approach adopted by Petrof et al., (1990), continuous positive airway pressure (CPAP) was used to reduce inspiratory muscle effort by counterbalancing PEEPi during constant workload cycle exercise. It was found that CPAP significantly reduced exertional dyspnea, and there was a highly significant correlation (r = 0.92) between the reductions in inspiratory muscle work (as measured by the pressure-time integral for esophageal pressure) and the reduction in dyspnea. Interestingly, the findings of Petrof et al., (1990) occurred without any change in EELV, which suggests that the reductions in dyspnea associated with a decrease in DH, are related to a reduction in inspiratory muscle activity rather than the DH *per se*.

Cardiovascular Limitations in COPD

In addition to the well-accepted pulmonary limitations to exercise, abnormal right ventricular (RV) (Mahler et al., 1984; Morrison et al., 1987; Matthay et al., 1992) and left ventricular (LV) function (Slutsky et al., 1981, Oelberg et al., 1998) have been reported in COPD patients. These atypical cardiac responses are likely related to the adverse lung mechanics associated with the disease (Ranieri et al., 1996). However, even though reductions in RV ejection fraction and LV end diastolic volume and stroke volume have been reported (Slutsky et al., 1981; Morrison et al., 1987), it is unclear whether these abnormal responses to exercise are of sufficient magnitude to significantly limit exercise tolerance.

In the absence of coronary artery disease, it is likely that the cardiovascular limitations seen with exercise in COPD originate on the right rather than the left side of the heart. The normal RV is a highly compliant chamber, with a thin lateral-wall and little ability to raise wall tension or pressure during systole (Klinger and Hill, 1991). During exercise, healthy lungs can easily accommodate large increases in RV stroke volume by distending already perfused capillaries and the recruitment of non-perfused vessels within the pulmonary vascular bed (Schulman and Matthay, 1992). Therefore, large increases in blood flow through the pulmonary vasculature can be accommodated with comparatively minimal elevation in pulmonary artery pressure (P_{pa}) and pulmonary vascular resistance (PVR) (Epstein et al., 1967). In contrast, the pulmonary vasculature of COPD patients is not easily recruited, and P_{pa} and PVR are often elevated at rest (Brent et al., 1982, 1984; Matthay et al., 1992). During exercise, even a small increase in pulmonary blood flow can result in a marked increase in P_{pa} and further elevation of PVR (Mahler et al., 1984). These acute elevations in P_{pa} and PVR impede RV output and only a small number of COPD patients are able to increase RVEF with exercise (Mahler et al., 1984; Morrison et al., 1987). Subsequently, any increase in RV stroke volume is only achieved during exercise by utilizing the Frank Starling mechanism and increasing RV preload (Matthay et al., 1992).

The mechanisms responsible for the elevated P_{pa} and PVR associated with COPD are not completely understood. However, alveolar hypoxia appears to be one of the primary candidates. In the systemic circulation a decrease in the partial pressure of arterial oxygen induces systemic vasodilation presumably to maximize oxygen delivery. However, in the pulmonary circulation, alveolar hypoxia induces vasoconstriction predominantly in the smaller pulmonary arteries or arterioles (Marshall and Marshall, 1983). Hypoxic vasoconstriction is normally a beneficial mechanism that diverts blood flow away from poorly ventilated lung regions, thereby optimizing alveolar ventilation-perfusion relationships and reducing shunt (Fishman, 1976). However, when alveolar hypoxia is present throughout the lung, as is the case in some COPD patients, hypoxic vasoconstriction leads to increased P_{pa} and PVR (Klinger and Hill, 1992).

Another mechanism that appears to contribute to the exercise-induced elevation in PVR and RV dysfunction in COPD patients is DH and the associated PEEPi. Whittenberger et al., (1960), demonstrated progressive increases in PVR accompanied inflation of the lung to higher volumes. This increase in PVR was due to marked increases in P_{pa}, while left atrial pressure only rose slightly and pulmonary blood flow decreased. To explain these observations further, the greater reductions in pleural pressure needed to overcome PEEPi and DH lead to approximately equal relative changes in alveolar pressure (Ranieri et al., 1996). When alveolar pressure exceeds pulmonary capillary intravascular pressure, the alveoli act as a Starling resistor compressing the pulmonary capillaries (Carden et al., 2000). Therefore, the alveolar pressure becomes the back pressure to flow (Permutt, 1961) and an increase in P_{pa}, similar to that in alveolar pressure is needed to maintain pulmonary blood flow (Ranieri et al., 1996). Thus the elevated alveolar pressure associated with DH and PEEPi increases RV impedance, and combined with any increase in PVR caused by hypoxia, may explain the failure of COPD patients to increase RV ejection fraction with exercise.

Dynamic hyperinflation can also directly compress the right heart and intrathoracic vessels, which increases RA pressure and reduces the gradient for venous return (Wright et al., 1983; Butler et al., 1988). In an opposing fashion, the large negative pleural pressure swings associated with breathing at high lung volumes and overcoming PEEPi are transmitted directly to the intrathoracic vasculature, decreasing RA pressure and enhancing the pressure gradient for venous return (Ranieri et al., 1996). Usually with forceful inhalations, the RA pressure decreases below atmospheric pressure and the large veins, such as the inferior vena cava collapse as they enter the thorax, reducing venous return (Nakhjavan et al., 1966). However, in dynamically hyperinflated COPD patients, the early part of inspiration is much like a Mueller maneuver, where large negative pressures are generated without a change in lung volume in order to overcome PEEPi (Ranieri et al., 1996). This results in an enhanced venous return without the compressive effects of the increased lung volume on right arterial pressure and the vena cava. Therefore, the large reductions in pleural negativity during inspiration associated with PEEPi appear to increase RV preload, which could affect LV compliance through diastolic ventricular interaction (Jardin et al., 1984).

Negative pleural pressure swings could also have a significant affect on LV and RV afterload. True ventricular afterload is defined as the stress acting on the ventricular wall during ventricular muscle shortening (Biernacki et al., 1988) and is a complex interaction between cavity area, transmural pressure and myocardial wall thickness. Theoretically, the large negative plural pressures generated on inspiration during exercise in COPD decrease the pressure surrounding the heart and elevate RV and LV transmural pressure (Bromberger-Barnea 1981). This increase in RV transmural pressure, coupled with the increase in RV cavity dimensions (Mahler et al., 1984), would increase RV wall stress and hence RV afterload unless considerable thickening of the ventricular wall occurs. Left ventricular afterload may also be elevated through the greater negative swing in pleural pressure increasing LV transmural pressure and transmural aortic pressures (Robotham et al., 1981). However, a definitive conclusion cannot be made on whether LV afterload is actually increased, as LV cavity dimensions and wall thickness have not been reported during exercise in this population.

The occurrence of ventricular interaction during exercise in COPD patients has yet to be investigated. However, the majority of studies that have measured cardiac dimensions and function at rest have found evidence of this phenomenon (Krayenbuehl et al., 1978; Jardin et al., 1984). Both Krayenbuehl et al., (1978) and Jardin et al., (1984), reported that enlargement of the RV, measured with two-dimensional echocardiography, was associated with decreased LV cavity dimensions at rest in COPD patients compared to normal controls. More recently, Boussuges et al., (2000) analysed Doppler transmitral and pulmonary venous flows to supply evidence of possible ventricular interaction in 34 patients with severe COPD and reported significant correlations between the filling patterns of the left atrium and LV, as well as RV pressure and diameter. In all of these studies however, resting LV systolic function at rest appeared unaffected by the reduced LV diastolic function. With exertion and DH, an increase in RV end diastolic volume (Mahler et al., 1984) may decrease the diastolic compliance of the left ventricle (Janicki and Weber, 1980). More specifically, the increase in RV end diastolic pressure that accompanies the increase in RV end diastolic volume would reduce the transeptal pressure gradient (Belenkie et al., 1983), shifting the interventricular septum to the left. This "flattening" and anterior movement of the ventricular septum, restricts early LV filling, prolongs isovolumic relaxation time (Louie et al., 1986) and could reduce LV end diastolic volume and stroke volume, unless an increase in LV contractility is observed.

In addition to the direct affect of lung mechanics on cardiac function, increased respiratory muscle work with exercise can also affect the delivery of cardiac output to the exercising muscles (Harms et al., 1997,1998). In healthy athletes and sedentary individuals, the respiratory muscles demand approximately 8-9 ml O_2. L^{-1} V_E (Martin and Stager, 1981) during heavy exercise. Therefore, 10-15% of total body VO_2 (Aaron et al., 1992) and 16-18% of the total cardiac output (Harms et al., 1998) is required to satisfy respiratory muscle demand. In patients with COPD, the inspiratory work of breathing is significantly increased due to DH and PEEPi and has been estimated to be approximately 35-50% of total body VO_2 (Levison and Cherniack, 1968; Alverti and Macklem, 2001).

Such a high O_2 demand would result in a considerable proportion of cardiac output being "stolen" from the exercising muscles, which would reduce exercise tolerance and contribute to the leg fatigue experienced by patients. Furthermore, Harms et al., (1997) demonstrated that a reduction in the work of breathing obtained via a proportional assist ventilator decreased respiratory muscle demand and increased blood flow to the locomotor muscles. Therefore, if breathing helium and/or hyperoxic mixtures can reduce the work of breathing in COPD patients, a greater percentage of the total available blood flow would be directed to the exercising muscles, which would increase O_2 supply and ultimately exercise tolerance.

The Effect of Hyperoxia on Exercise Tolerance in COPD

The benefits of oxygen therapy in COPD patients have been well documented and have been shown to improve survival, reduce pulmonary hypertension, and improve exercise capacity and quality of life (NOTG, 1980; Morrison and Stovall, 1992; Zielinski et al., 1998). A number of studies have also demonstrated that acute oxygen administration markedly improves exercise tolerance in hypoxemic patients (Swinburn et al., 1991; Mitlehner and Kerb, 1994). However, the improvements in exercise tolerance with hyperoxia correlate poorly with enhanced arterial PO2 (Bradley et al., 1978), which suggest that other mechanisms are also responsible for the improved exercise capacity with increased O_2. O'Donnell et al., (2001b) reported that symptom limited exercise endurance time was increased with hyperoxia by approximately 115% in severe COPD patients who qualified for ambulatory oxygen therapy. At a standardized time during exercise, dyspnea, V_E and breathing frequency were all significantly decreased. The decrease in ventilatory demand resulted in reduced mid-expiratory flow rates and EILV, while EELV was maintained nearer to resting levels. O'Donnell and colleagues conclude that the improved exercise endurance times with hyperoxia were due to the effect of hyperoxia on ventilatory drive, improved ventilatory mechanics, delayed ventilatory constraints and dyspnea alleviation. .

In contrast, relatively little research has addressed the effects of hyperoxia for patients who do not qualify for O_2 supplementation. O'Donnell et al., (1997b), found that 60% O_2 increased endurance time to exhaustion by 35 ± 11% in mild to moderate hypoxemic COPD patients. The improvements in endurance time significantly correlated with reductions in dyspnea ($r = -0.64$, $p<0.05$) and there was a proportional relationship between changes in ventilation and ratings of exertional breathlessness (O'Donnell et al., 1997b). Complementary to the studies of O'Donnell et al., (1997b, 2001b), Somfay et al., (2001) also reported that hyperoxia ($F_IO_2 = 0.3$) reduced EELV, EILV, dyspnea rating, breathing frequency and V_E compared to breathing air. EELV and EILV negatively correlated with endurance time and the decrease in exercise breathlessness correlated with the decrease in breathing frequency. Collectively, these results demonstrate that in patients who do not qualify for ambulatory O_2 therapy, hyperoxia reduces ventilatory demand, alleviates dyspnea and improves exercise tolerance, likely through beneficial changes in operational lung volume and breathing pattern.

It is possible that the improved lung mechanics seen with hyperoxia also have a positive affect on cardiovascular function in COPD. Fujimoto et al., (2002) demonstrated that oxygen delivered at 2 $L.min^{-1}$ to COPD patients with varying levels of airway obstruction, decreased P_{pa} and PVR and increased the distance walked in six minutes.

The authors stated that a reduction in hypoxic vasoconstriction with hyperoxia was at least partly responsible for the decrease in P_{pa}, as oxygen administration almost completely prevented the increases in PVR associated with exercise. However, they also reported that reductions in air trapping index with hyperoxia were positively correlated with a reduced pulmonary capillary wedge pressure. This suggests that reductions in DH with hyperoxia are responsible for the decreases in pulmonary capillary wedge pressure, which likely contribute to the reduced P_{pa} observed during exercise with this gas. Few other studies have addressed the potential benefits of hyperoxia on cardiovascular function and exercise tolerance in COPD patients. However, if the reductions in ventilatory demand and DH with oxygen can decrease P_{pa}, PVR and pulmonary capillary wedge pressure, then it is also possible that hyperoxia will improve RV ejection fraction, decrease RV end diastolic volume and reduce any diastolic ventricular interaction that occurs during exercise.

The Effect of Helium on Exercise Tolerance in COPD

Previous research has shown that HE-OX reduces dyspnea in emphysema patients (Barach, 1934), decreases pulmonary resistance (Grape et al., 1960) and reduces the non-elastic work of breathing in dogs with central airway obstruction (Barnett et al., 1967). More recently, other studies have demonstrated that helium-oxygen mixtures can significantly reduce trapped air volume (Tassaux et al., 2000), work of breathing (Jaber et al., 2000), P_aCO_2 (Jaber et al., 2000) and the negative swings in pleural pressure on inspiration (Manthous et al., 1995) associated with acute exacerbations of COPD.

Through the mechanisms mentioned above, it is also possible that helium-oxygen mixtures improve exercise tolerance in COPD patients. To date, only three known studies have addressed this interesting topic and these studies have reported mixed results. In the first study, Bradley et al. (1980) demonstrated that normoxic-helium has no effect on the peak oxygen consumption (VO_{2peak}) of patients with severe COPD. However, Bradley and colleagues used an exercise protocol that did not allow changes in VO_{2peak} to be clearly identified and so the conclusions of this study may not be wholly accurate. In contrast, two more recent investigations by Oelberg et al., (1998) and Richardson et al., (1999b) demonstrated that VO_{2peak} can be improved with normoxic helium mixtures. Oelberg and coworkers (1998) administered normoxic-helium to ten very severe COPD patients (FEV_1 = 19%pred) during cycle exercise to exhaustion. HE-OX increased maximal ventilation (31%), arterial saturation (85 vs. 88 %) and VO_{2peak} by 16%. The increase in VO_{2peak} occurred without a significant increase in cardiac output (5.6 $L{\cdot}min^{-1}$ vs. 5.9 $L{\cdot}min^{-1}$ in air and HE-OX, respectively), even though there was a significant (21.5%) reduction in PVR and a non-significant (9.5%) decrease in P_{pa}. Richardson et al., (1999) recruited patients with less severe COPD and demonstrated that breathing a normoxic-helium mixture increased VO_{2peak} (17.9%), peak ventilation (28.6%) and peak power output (15.5%), without any improvement in S_aO_2. The authors suggest that the enhanced VO_{2peak} with HE-OX is a result of greater peripheral O_2 availability and improved perfusion of the working muscles due to a reduction in the O_2 demand of the respiratory musculature.

Even though the studies of Oelberg et al., (1998) and Richardson et al., (1998) demonstrate that HE-OX can improve VO_{2peak} in COPD patients, the effects of breathing normoxic-helium on expiratory flow limitation, operational lung volumes, work of breathing, cardiovascular function and exercise tolerance have not been studied. Theoretically, reductions in dynamic hyperinflation, PEEPi and work of breathing combined with an enhanced ventilatory capacity could reduce exertional breathlessness and positively impact cardiovascular function and exercise tolerance.

The Effect of Helium-Hyperoxia on Exercise Tolerance in COPD

Unlike helium, hyperoxia does not have the ability to increase maximal expiratory flow rate or increase ventilatory capacity. As a result, when V_E reaches the peak values achievable with air, comparable levels of dyspnea and exercise are experienced. In contrast, normoxic-helium gas mixtures have been shown to increase the maximal-flow volume loop in COPD (Libby et al., 1981), which could reduce expiratory flow limitation and DH, while improving ventilatory capacity. However, due to the resistive unloading with HE-OX, V_E is increased and COPD patients have been reported to perceive a similar level of dyspnea to normal air breathing (Richardson et al., 1999), which may still terminate exercise prematurely.

To the author's knowledge, no research has investigated the use of helium-hyperoxia on the exercise tolerance of COPD patients. Theoretically, during submaximal exercise hyperoxia will decrease ventilatory demand and increase expiratory time, while helium will increase expiratory flow rates. Taken together, these interventions would greatly reduce DH, inspiratory muscle effort and dyspnea. A reduction in DH may also have a significant effect on cardiovascular function by reducing P_{pa}, PVR and improving RV ejection fraction. Moreover, a decrease in EELV and PEEPi would reduce the negative pleural pressure swings needed on inspiration, which would reduce RV preload and afterload. In combination, helium-hyperoxia could greatly improve RV function, which may improve LV filling and LV systolic function by decreasing diastolic ventricular interaction.

Summary

It is evident that the self-contained breathing apparatus reduces exercise capacity by imposing a resistance to expiration. However, the extent of this EFL and the impact on V_E and VO_{2max} has not been studied. Furthermore, although the benefits of hyperoxia for improving VO_{2max} while wearing the SCBA have been documented, the effects of lower density helium-oxygen gas mixtures on EFL, V_E and VO_{2max} are currently unknown.

Patients with COPD are more severely affected by EFL, ventilatory impairment and dyspnea than healthy individuals wearing the SCBA. Therefore, if a helium-oxygen mixture can improve the exercise capacity of individuals wearing an external imposed EFL, then it may have even greater benefits on the physiologically imposed EFL of COPD patients. Theoretically, if a hyperoxic-helium gas mixture can combine the benefits of a lower density gas with those of a higher fraction of oxygen, it could potentially have a greater positive influence on pulmonary mechanics, cardiovascular function, dyspnea and exercise tolerance than either normoxic-helium or hyperoxia.

Statement of Purpose

The overall purpose of the research performed for this thesis was to determine the effect of helium based gas mixtures for improving the VO_{2max} of individuals wearing the SCBA and the exercise tolerance of COPD patients. To achieve this aim, three separate studies were performed. The first study was designed to determine if the externally imposed expiratory resistance of the SCBA attenuates V_E and VO_{2max}. A second study then looked at the benefits of normoxic and hyperoxic helium-based gas mixtures for reducing these ventilatory constraints and improving VO_{2max}. Finally, the aimof the third study was to investigate if the helium gas mixtures used in the second study could also improve the pathophysiological ventilatory constraints associated with COPD and enhance exercise tolerance.

Study One

Before investigating the effects of helium based gas mixtures for improving the exercise capacity of SCBA wearers, it was important to document the effect of the modern SCBA commonly worn by firefighters on ventilation and maximal oxygen consumption. Therefore, the first study addressed the following two hypothesis:

1) Modern self-contained breathing apparatus will reduce V_E and VO_{2max}.
2) The SCBA breathing regulator will be responsible for the reductions in VO_{2max} observed.

The findings of this study are summarized in Chapter II.

Study Two

Based on the findings of the first study, a second investigation was designed to investigate whether helium based gas mixtures with varying levels of oxygen could reduce the external expiratory breathing resistance of the SCBA regulator and improve maximal oxygen consumption and ventilatory responses to exercise at submaximal work loads. The study was designed to test the following hypotheses:

1) Hyperoxia, normoxic-helium and helium-hyperoxia will significantly reduce the external breathing resistance imposed by the SCBA and increase VO_{2max} compared to breathing compressed air. Furthermore the improvements in VO_{2max} with helium-hyperoxia will be significantly greater than either normoxic-helium or hyperoxia alone.
2) Helium-based gas mixtures with varying levels of oxygen will significantly reduce external breathing resistance during sustained submaximal exercise with the SCBA.

The findings of this study are summarized in Chapter III and IV, respectively.

Study Three

Based on the findings of the second study a final investigation was undertaken to investigate the potentially greater benefits of breathing a helium-hyperoxic gas mixture on dynamic hyperinflation, cardiovascular function, dyspnea and exercise tolerance in patients with chronic obstructive pulmonary disease. The study was again designed to test the following hypothesis:

1) Helium-hyperoxia will increase exercise tolerance to a greater extent than hyperoxia or normoxic helium in COPD patients.
2) Helium-hyperoxia will have a greater effect on dynamic hyperinflation, work of breathing and dyspnea than HOX or HE-OX
3) Helium-hyperoxia will have a greater effect on LV end-diastolic cavity and LV systolic function than both the other gas mixtures.

The findings of this study are summarized in Chapter V

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CHAPTER II

The Influence of Self-Contained Breathing Apparatus (SCBA) on Ventilatory Function and Maximal Exercise Performance.

Introduction

One of the primary components of the protective ensemble worn by firefighters is the self-contained breathing apparatus (SCBA), which provides protection from inhaling smoke, ash and other airborne pollutants. However, previous research (Louhevaara et al., 1984) has demonstrated that during heavy work the SCBA attenuates minute ventilation and greatly reduces maximal exercise performance (Louhevaara et al. 1985, 1986; Raven et al., 1977). This ventilatory limitation is likely due to the added resistance to expiration imposed by the expiratory valves of the SCBA regulator (Louhevaara et al., 1984). However, Louhevaara and colleagues (1985) also postulate that the weight of the SCBA cylinder and the shoulder straps of the cylinder harness also hinder chest wall mechanics.

Since these earlier studies, SCBA technology has improved and it is possible that ventilatory limitation is no longer important. However, we recently reported that breathing lower density gas mixtures through the SCBA increased maximal minute ventilation (V_E) and improved maximal oxygen consumption (VO_{2max}) (Eves et al., 2003a). These findings suggest that at heavy workloads even the modern SCBA imposes an external expiratory load sufficient to decrease work performance. Therefore, the aim of this study was to determine the magnitude of ventilatory limitation caused by the

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present day SCBA and its impact on VO_{2max} compared to the standard laboratory practice of breathing through a low resistance two-way valve. Furthermore, by separating the SCBA into its individual components (e.g. breathing regulator or cylinder and harness assembly), we investigated the relative importance of each of these components in reducing VO_{2max}.

Methods

Participants

Twelve healthy, active male participants, who had previously completed similar graded exercise protocols with the SCBA, volunteered for the study. Participants were informed of all aspects of the study before providing written informed consent, which had previously received institutional ethics review board approval. Participant characteristics were as follows (mean ± SD): mass 79.7 ± 8.5kg; age 28.0 ± 6.6yr and height 178.2 ± 3.6cm.

Experimental Design

During a two-week period, each participant completed four maximal graded exercise tests to study the effect of the individual components of the SCBA on maximal exercise performance. The exact conditions of each trial were as follows 1) Control trial (CON*)* – Participants breathed through a low resistance two-way breathing valve (Hans Rudolph 2700, Kansas City, MO) and *did not* carry the SCBA air cylinder. 2) Full SCBA trial (SCBA) – Participants carried the SCBA air cylinder assembly (consisting of air cylinder, harness and backframe) and breathed through the SCBA regulator. 3) Regulator only trial (REG) - Participants breathed through the SCBA regulator but *did not* carry the

SCBA air cylinder. 4) SCBA air cylinder trial (PACK) - Participants breathed through the low resistance two-way breathing valve and carried the SCBA air cylinder assembly. All tests were randomized and separated by at least 48 hours.

For each test, participants wore shorts, T-shirt, running shoes and the National Fire Protection Association standard 1500 jacket (Safeco Manufacturing, Scarborough, ON). The protective jacket was worn in all tests to improve comfort when carrying the SCBA cylinder assembly and to standardize conditions when no cylinder was carried. For the SCBA and REG trial the compressed air mixture was delivered to the subjects from K-sized cylinders standing adjacent to the treadmill. The gas was prepared according to medical gas standards and had been chemically analyzed in the manufacturer's laboratory (Praxair Canada Inc., Edmonton, AB).

Self-Contained Breathing Apparatus

The Scott 4.5 SCBA was used in this investigation (Scott Health and Safety, Monroe, NC). This particular model of SCBA is currently in use by many fire departments and is representative of modern SCBA technology. The SCBA consisted of a Kevlar® cylinder and valve assembly; a harness and back frame; an automatic dual path redundant pressure-reducing regulator; a full face piece and a removable, facepiece-mounted positive-pressure breathing regulator (SCOTT PRESUR-PAK®, E-Z FLO™). Inactivation of the air-saver switch, low-pressure alarms and purge valves were the only changes made to the experimental SCBA over those used in the field. All of the SCBA components used in this research were maintained within the manufacturer's specifications by a qualified Scott technician. The total weight of the SCBA used in this study was 12.1 ± 0.5kg. The weight of the cylinder assembly without the mask and breathing regulator was 11.7 ± 0.4kg

Incremental Exercise Tests

Protocol

VO_{2max} was determined by walking on a motorized treadmill (Quinton Instruments, Model 18-60, Seattle, WA). Participants walked at a constant speed (3.5 or 4.0 mph) and grade was increased at increments of 2% every two minutes until ventilatory threshold, which was detected by a systematic increase in the V_E/VO_2 ratio, while V_E/VCO_2 remained constant or declined slightly (Wasserman, 1987; Eves et al., 2003a). The grade was then increased 2% every minute until exhaustion. The highest 30 second VO_2 value was accepted as VO_{2max}. Maximal power output was then calculated using the following equation [mass x speed x grade].

Physiological Measurements

Expired gases and ventilatory parameters (minute ventilation, tidal volume and breathing frequency) were measured when breathing from the SCBA regulator or the Hans-Rudolph valve using a metabolic measurement system (SensorMedics Horizon, Yorba Linda, CA). The experimental set-up used to collect expired gases with the SCBA has previously been described (Eves et al., 2002a). Briefly, a plexiglass cone was designed to fit over the exhalation ports of the SCBA regulator to duct expired gas to the mixing chamber of the metabolic measurement system. The length of gas collection tubing used was identical in each trial to control the external breathing resistance of the breathing circuit. Heart rate and oxyhemoglobin saturation (S_pO_2) were measured continuously using telemetry (Polar Beat, Polar Electro, Lachine, PQ) and pulse oximetry (SensorMedics, Yorba Linda, CA). This technique to measure S_pO_2 has previously been validated during exercise (Mengelkoch et al., 1994).

Mouth Pressures

Peak expiratory mouth pressures were measured at the end of each workload using a differential pressure transducer (MP45, Validyne, Northridge, CA). Pressures from the transducer were amplified and recorded on a calibrated high-speed chart recorder (Gould, Cleveland, OH). In the SCBA and REG trials, the transducer was connected to the face piece by tubing attached to a metal disc that replaced the cover of the mask voice port. In the CON and PACK trials the same tubing was attached to a small nipple mounted near the mouthpiece of the Hans-Rudolph valve. The reported peak expiratory pressures were the mean of five consecutive ventilatory cycles. Mean expiratory flow was calculated from tidal volume and expiratory time (tidal volume/ expiratory time) and then used to estimate external breathing resistance during expiration (expiratory mouth pressure/ mean expiratory flow).

Psychophysical Measurements

Psychophysical measurements were recorded at five-minute intervals during each trial. Ratings of perceived exertion (RPE) were measured using the 15-point Borg scale (Borg et al. 1982). Perceived respiratory distress (PRD) was measured using a modified version of the 7-point psychophysical scale described previously (Morgan and Raven 1985; Eves et al., 2003b).

Statistical Analysis

All dependent variables measured during maximal exercise under the four experimental conditions were compared using a repeated measures ANOVA. A Tukey post-hoc multiple comparisons test was used if the ANOVA demonstrated a significant outcome. To ascertain any association between changes in maximal oxygen consumption and maximal ventilation, simple regression analysis using Pearson correlations were performed. The same analysis was also used to explore whether there was any relationship between changes in expiratory flow with the SCBA and expiratory breathing resistance. An alpha level set *a priori* at 0.05 was considered significant for all analysis and post hoc tests.

Results

Physiological and Psychophysical Responses to Maximal Exercise

The physiologic responses to maximal exercise are shown in Table II-1. The SCBA significantly reduced maximal oxygen consumption, ventilation and maximal power output compared to a standard low resistance-breathing valve. The attenuated ventilation with the SCBA was due to a significant reduction in tidal volume while breathing frequency remained unchanged. Duty cycle or T_I/T_{TOT} (where T_I is the inspiratory time and T_{TOT} is the total time of one ventilatory cycle) was significantly decreased with the SCBA due to both a reduction in T_i and an increase in expiratory time

(T_E). At maximal exercise, breathing resistance and peak expiratory pressure were significantly increased in the SCBA trial, while maximal expiratory flow rate was reduced. It should be mentioned, that the breathing resistance reported in Table II-1 combines the resistance of the SCBA, the gas collection hoses and metabolic measurement system. As the resistance of the breathing circuit was the same in all trials the SCBA regulator is solely responsible for the differences observed in breathing resistance.

While the SCBA condition had the largest effect on exercise performance, the two individual components of the SCBA also had significant effects (Table II-1). Compared to CON, maximal oxygen consumption was reduced in both the PACK and REG conditions. However, the decrease in VO_{2max} was significantly greater in the REG compared to the PACK trial. Peak power output was also significantly reduced in REG compared to CON, but not the PACK condition. At maximal exercise there were no significant differences in any of the ventilatory responses to exercise between PACK and CON. Conversely, REG decreased ventilation, and inspiratory time, and increased expiratory time without significantly changing tidal volume or breathing frequency. REG also increased external expiratory breathing resistance, decreased peak expiratory flow rate and increased expiratory pressure compared to both the CON or PACK trials.

At peak exercise, oxyhemoglobin saturation was decreased in the SCBA and REG trials compared to the PACK and CON conditions. Maximal heart rate and the rating of perceived exertion (RPE) were not significantly different in any trial. Moreover, despite an increase in breathing resistance and expiratory pressure, participants perceived their respiratory distress to be similar at maximal exercise in all four conditions. However, it should be reiterated that these responses occurred at a lower power output in the REG and SCBA trials.

Ventilatory Responses to Incremental Exercise.

Comparisons of the ventilatory responses to incremental exercise between the CON and SCBA conditions are presented in Figures 1 and 2. As the REG and PACK tests did not differ from the SCBA and CON trials, respectively, only the latter conditions were used in this analysis. During incremental exercise, minute ventilation increased in a similar fashion in both the SCBA and CON conditions and there was no significant difference in ventilation at power outputs up to 240W, which was the last power output that all twelve participants completed (Figure II-1A). However, at a comparable ventilation during each incremental test, a different breathing pattern was adopted when breathing from the SCBA compared to the low-resistance breathing valve (Figures II-1B and II-C). In the SCBA trial tidal volume was increased and breathing frequency was decreased at the lower ventilation rates, whereas at high ventilation rates, tidal volume was significantly decreased and breathing frequency was unchanged from CON. In addition, duty cycle was significantly reduced at ventilations above 80 $L \cdot min^{-1}$ mainly due to a reduced T_I, although at 100 $L \cdot min^{-1}$ and at maximal exercise this was also due to an increased T_E.

Figure II-2A demonstrates that expiratory flow was not significantly different with the SCBA at any ventilation other than at maximal exercise. However, at ventilations above 80 $L \cdot min^{-1}$ there was a significantly greater external expiratory breathing resistance and an elevated expiratory mouth pressure with the SCBA (Fig. II-2B and II-2C).

Discussion

The Effect of the SCBA on Maximal Exercise Performance

This study confirmed that the modern SCBA commonly used by firefighters decreases maximal oxygen uptake. The SCBA decreased VO_{2max} by 14.9 ± 7.1% and maximal power output by 11.6 ± 8.2%, compared to breathing through a low resistance breathing valve. The added expiratory resistance imposed by the breathing regulator was predominantly responsible for the decrease in maximal exercise performance, as VO_{2max} in the REG trial (13.1 ± 4.6%) was reduced to a similar extent as the full SCBA condition. Carrying the SCBA cylinder assembly also reduced VO_{2max} (4.8 ± 5.3%). However, this reduction was significantly less than in the REG condition, suggesting that the harness straps and air cylinder weight only minimally restrict ventilation, even during maximal work.

At maximal exercise, the SCBA reduced ventilation and altered the normal breathing pattern observed during the CON trial. This attenuated minute ventilation was due to a decrease in tidal volume since breathing frequency was not different between conditions. Expiratory mouth pressure was significantly elevated in an attempt to maintain flow and overcome the greater breathing resistance imposed by the SCBA regulator. In the REG trial, tidal volume was not significantly reduced ($p=0.09$), but breathing resistance was still increased. These findings, in combination with the reduced duty cycle in both the SCBA and REG trials, demonstrate that the SCBA regulator imposes a significant obstruction to expiration at high ventilation rates. Furthermore, it appears that the external breathing resistance imposed by the SCBA regulator is responsible for the reduction in VO_{2max} as there was a significant correlation between the reduction in maximal ventilation and the attenuation of VO_{2max} with the SCBA (Figure II-3).

The findings of the present study are similar to those previously reported where an externally imposed breathing resistance was used to reduce expiratory flow rates. (Kayser et al., 1997; Iandelli et al., 2002). These previous studies, like our study, demonstrated a significant reduction in exercise capacity and ventilation, with similar changes in breathing pattern and duty cycle. In the presence of increased expiratory resistance, a number of factors could be responsible for the attenuated exercise performance such as dynamic hyperinflation (O'Donnell et al., 1997; 1998 Murciano et al., 2000; Diaz et al., 2000), intrinsic inspiratory threshold loading (Dal Vecchio et al., 1990; Tschernko et al., 1998; Chen and Yan, 1999), an increase in the elastic work of breathing due to hyperinflation (Yan et al., 1997), severe dyspnea (Killian and Jones, 1988; O'Donnell et al., 1993, 1997) and a reduction in arterial oxygen saturation due to inadequate ventilation (Dempsey et al., 1984, 2003). Unfortunately, due to the design of the SCBA, inspiratory capacity could not be determined during exercise in this study so we do not know if dynamic hyperinflation occurred. However, the finding that maximum tidal volume peaked at a lower ventilation with the SCBA compared to CON supports the notion that dynamic hyperinflation occurred, limiting ventilation and decreasing VO_{2max}. On the other hand the decrease in T_I/T_{TOT} observed with the SCBA may indicate that the subjects exhaled longer in the SCBA and REG trials to maintain end-expiratory lung volume and prevent dynamic hyperinflation. Oxyhemoglobin saturation decreased in all trials, falling approximately 5-7% from resting levels at maximal exercise. The extent of desaturation was greater in both the REG and SCBA trials compared to PACK and CON. However, the mean difference between the SCBA, REG and CON trials was only 1-2%, which is unlikely to have a significant additional effect on VO_{2max} (Dempsey et al., 2003).

During the SCBA trial we observed a wide variety of individual ventilatory responses. Figure II-4A demonstrates that compared to CON, the reduction in maximal ventilation with the SCBA ranged from 2.5 $L \cdot min^{-1}$ to 24.5 $L \cdot min^{-1}$. This suggests that some individuals are able to generate similar ventilations on the SCBA despite the increase in expiratory breathing resistance. The size and aerobic fitness levels of the participants may partially explain these individual differences as a significant relationship was found between the change in ventilation with the SCBA and the absolute VO_{2max} of each participant in the control condition ($r = 0.69$, $p<0.05$, Figure II-4B). A few studies have demonstrated that aerobically trained individuals have greater respiratory muscle strength (Fuso et al., 1996) and endurance (Eastwood et al., 2001) than lesser-trained individuals. Therefore, it is feasible that those individuals with a higher VO_{2max} can generate and maintain the greater pressures necessary to maintain maximal flow rates. The significant relationship ($r=0.69$, $p<0.05$) between peak expiratory pressure and the flow rate at maximal exercise makes this postulate more attractive (Figure II-4C). In applications such as firefighting, these findings could be of importance, as the added external breathing resistance has a greater negative effect on smaller and/or less aerobically fit individuals when performing high intensity work.

2.4. The Effect of the SCBA on Incremental Exercise

During the last decade, SCBA technology has improved. The modern regulator used in this study maintains a positive pressure within the face piece and guarantees inspiratory assistance even at maximal exercise. There have also been advances in harness design for comfort and better weight distribution. The cylinder itself is made of lighter material such as aluminum and then covered by either carbon or Kevlar®. In the present study, there was no effect of the SCBA on ventilation below 110 L·min^{-1}. These findings are different from the studies of Louhevaara et al., (1985) who demonstrated that earlier generation demand-type SCBA regulators increased ventilation rates during submaximal exercise (~60L·min^{-1}) but caused significant ventilation impairment at maximal exercise. More specifically, Louhevaara and colleagues (1985) reported that, at exercise termination with the SCBA, VO_2 was reduced 17.2% and maximal ventilation was decreased 32%, which resulted in a 40.8% reduction in VCO_2. As 110 L·min^{-1} was the last ventilation that all 12 subjects achieved it is difficult to say at precisely what ventilation the expiratory breathing resistance becomes a limiting factor. However, as mean expiratory flow rates were reduced at maximal exercise, the expiratory breathing resistance effects expiratory flow somewhere above 110 L·min^{-1} or at an intensity above 87% of the VO_{2max} achievable on the SCBA and above 75% of the VO_{2max} achieved in the control condition.

The average cost of performing firefighting work has previously been described (Sothmann et al., 1990, Gledhill and Jamnik, 1995; Bilzon et al., 2001). By averaging the oxygen consumptions reported from these studies it would appear that 35 ml·kg^{-1}·min^{-1} would be needed to perform the individual tasks associated with this occupation.

Assuming the average mass of a North American firefighter to be ~83kg (Horowitz and Montgomery, 1993) and the average ventilation to VO_2 ratio (V_E/VO_2) during prolonged exercise with the SCBA to be 30 (Eves et al., 2002), a ventilation of approximately 90 $L{\cdot}min^{-1}$ would be adequate to perform the majority of firefighting tasks. It can therefore be assumed that modern SCBA do not have a significant affect on the exercise capacity of firefighters. However, if a sustained bout of high intensity work was needed this conclusion may not be accurate.

2.5 Summary

In summary, the modern SCBA worn by firefighters decreases VO_{2max} and peak power output due to a ventilatory limitation imposed by the added expiratory breathing resistance of the SCBA regulator. However, the SCBA harness and weight of the air cylinder also play a small role in this limitation by adding a slight restrictive load to the thoracic wall. During graded exercise, expiratory flow rate and minute ventilation appear to be sufficient with the SCBA even with the elevated expiratory breathing resistance. These observations establish that at exercise intensities comparable to the majority of firefighting tasks, the modern SCBA does not impose a significant limitation to ventilatory function. However, it may decrease the work capacity of some individuals, especially those with a reduced VO_{2max}, if there is a necessity to produce high or maximal bouts of work.

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TABLE II-1: Maximal Exercise Responses

	Condition			
Variable	**CON**	**SCBA**	**REG**	**PACK**
VO_2, L·min^{-1}	4.19 ± 0.41^{bcd}	3.63 ± 0.46^{ad}	3.69 ± 0.35^{ad}	3.98 ± 0.42^{acb}
VO_2, ml·kg^{-1}·min^{-1}	52.6 ± 7.4^{bcd}	46.0 ± 7.0^{ad}	46.6 ± 6.6^{ad}	50.3 ± 7.7^{acb}
Power Output, W	330 ± 35^{bc}	297 ± 32^{a}	309 ± 33^{a}	314 ± 32
VCO_2, L·min^{-1}	5.20 ± 0.42^{bc}	4.54 ± 0.52^{ad}	4.49 ± 0.44^{ad}	5.01 ± 0.47^{bc}
RER	1.24 ± 0.06	1.26 ± 0.05	1.22 ± 0.06^{d}	1.26 ± 0.05^{c}
V_E, L·min^{-1}	171.3 ± 16.9^{bc}	160.8 ± 22.2^{a}	160.7 ± 21.3^{a}	165.7 ± 21.1
Tidal Volume, L	2.86 ± 0.30^{b}	2.66 ± 0.22^{a}	2.74 ± 0.30	2.75 ± 0.30
Breathing Frequency	60 ± 7	61 ± 8	59 ± 8	60 ± 8
T_I/T_{TOT}	0.46 ± 0.04^{bc}	0.40 ± 0.03^{ad}	0.40 ± 0.03^{ad}	0.47 ± 0.41^{bc}
P_E, cm H_2O	16.2 ± 3.7^{bc}	20.3 ± 3.6^{ad}	20. 2± 4.4^{ad}	16.4 ± 3.5^{bc}
V_T/T_E, L·s^{-1}	6.0 ± 1.0^{bc}	5.1 ± 0.8^{ad}	5.1 ± 0.9^{ad}	6.0 ± 1.4^{bc}
BR, cm H_2O·L^{-1}·s^{-1}	2.7 ± 0.4^{bc}	4.0 ± 0.6^{ad}	4.0 ± 0.6^{ad}	2.8 ± 0.4^{bc}
HR, beats·min^{-1}	191 ± 5	189 ± 5	190 ± 5	190 ± 6
RPE	19.0 ± 0.4	19.2 ± 0.6	19.1 ± 0.5	19.3 ± 0.5
PRD	5.2 ± 0.8	5.6 ± 0.6	5.6 ± 0.8	5.1 ± 0.9
S_pO_2, %	91 ± 2^{bc}	90 ± 2^{ad}	90 ± 2^{ad}	92 ± 2^{bc}

Values are means ± SD. *Abbreviations:* VO_2 = oxygen consumption, VCO_2 = carbon dioxide produced, RER = respiratory exchange ratio, V_E = ventilation, T_I/T_{TOT} = duty cycle (inspiratory time/total time), P_E = expired mouth pressure, V_T/T_E = mean expiratory flow, BR = external breathing resistance during expiration, HR = heart rate, RPE = rating of perceived exertion, PRD = perceived respiratory distress, S_pO_2 = oxyhemoglobin saturation. [a] = different from CON, $p<0.05$; [b] = different from SCBA, $p<0.05$; [c] = different from REG, $p<0.05$, [d] = different from PACK, $p<0.05$.

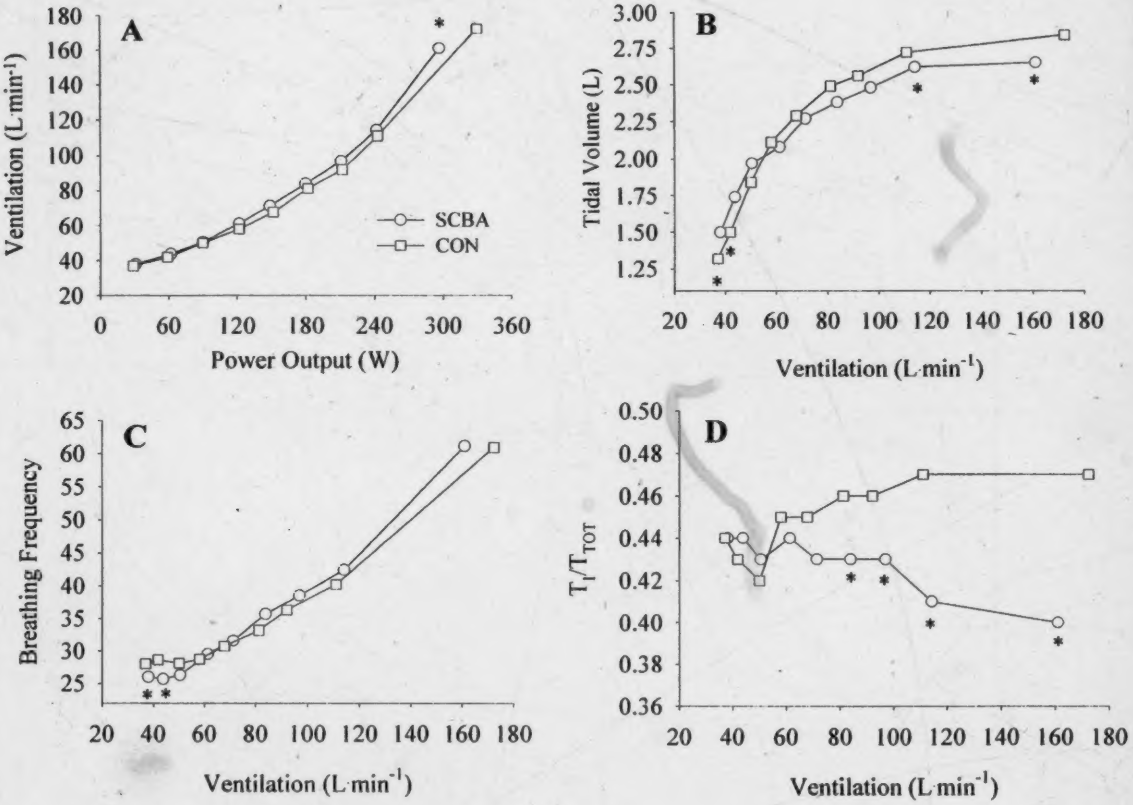

Figure II-1: The ventilatory response to graded exercise (A). The tidal volume and breathing frequency responses at comparable ventilations (B & C). Variations in duty cycle (T_I/T_{TOT}) at comparable ventilations (D). As ventilation was significantly greater in the CON trial at the termination of the graded exercise test, the final comparison is made between the peak exercise values. n=12 for all data points. * = $p<0.05$, SCBA vs. CON.

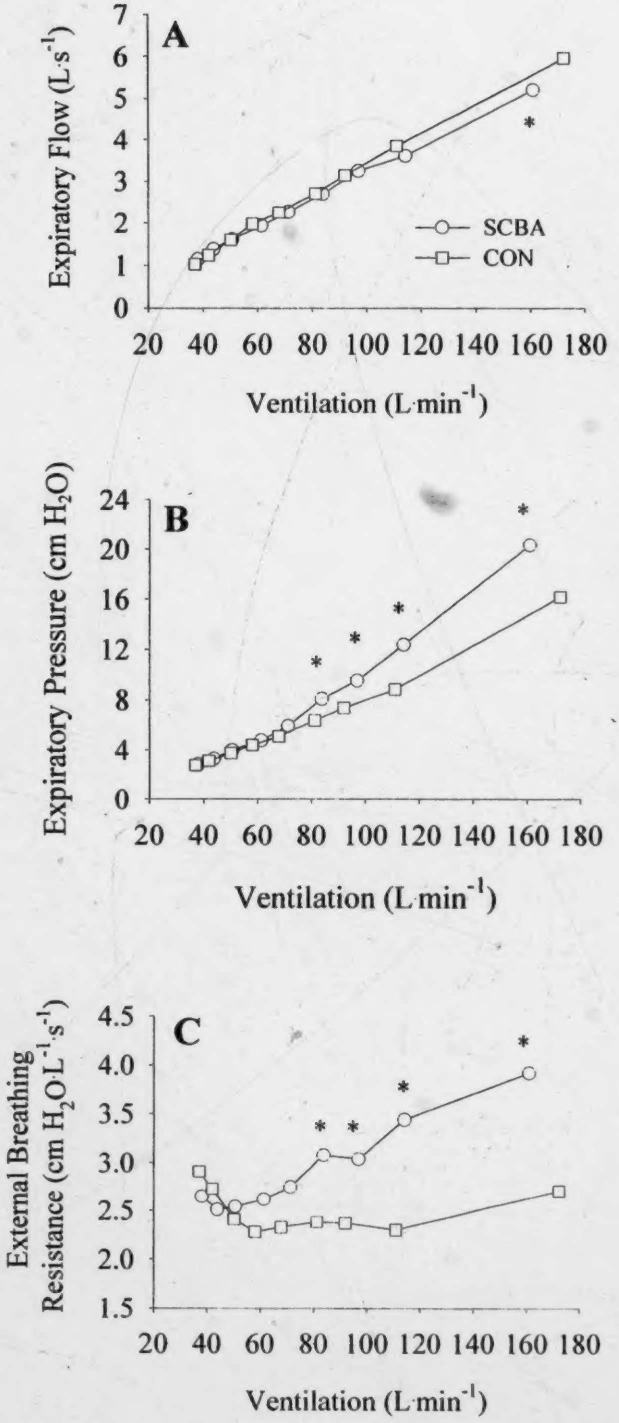

Figure II-2: The expiratory flow (A), mouth pressure (B) and breathing resistance (C) responses at comparable ventilations. As ventilation was significantly greater in the CON trial at the termination of the graded exercise test, the final comparison is made between the peak exercise values. n=12 for all data points. * = $p<0.05$, SCBA vs. CON.

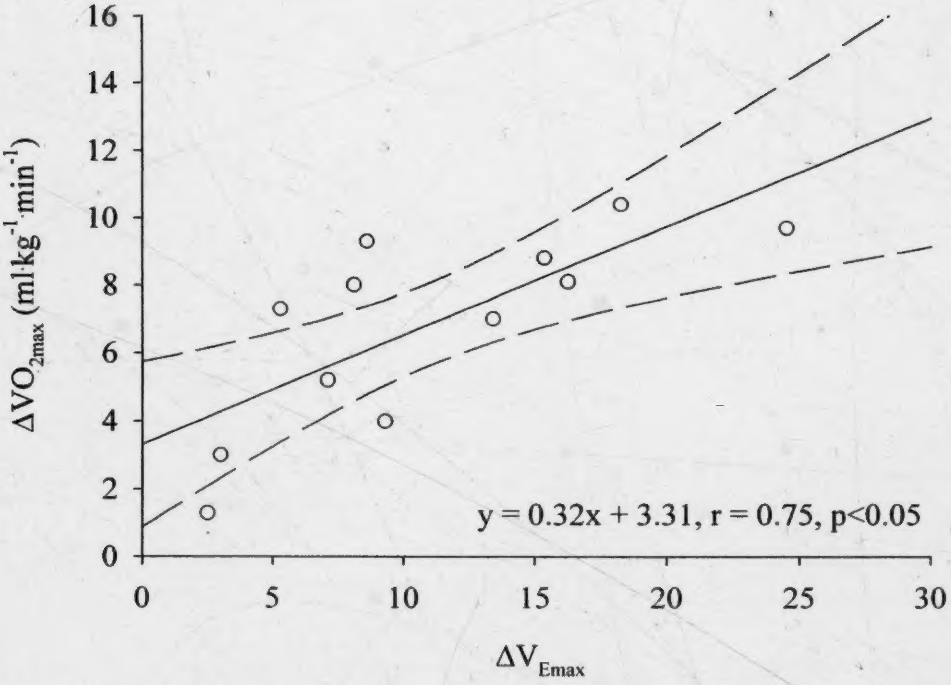

Figure II-3. The relationship between the reduction in maximal V_E (ΔV_{Emax}) and the decrease in maximal oxygen consumption (ΔVO_{2max}) observed with the SCBA compared to the control condition.

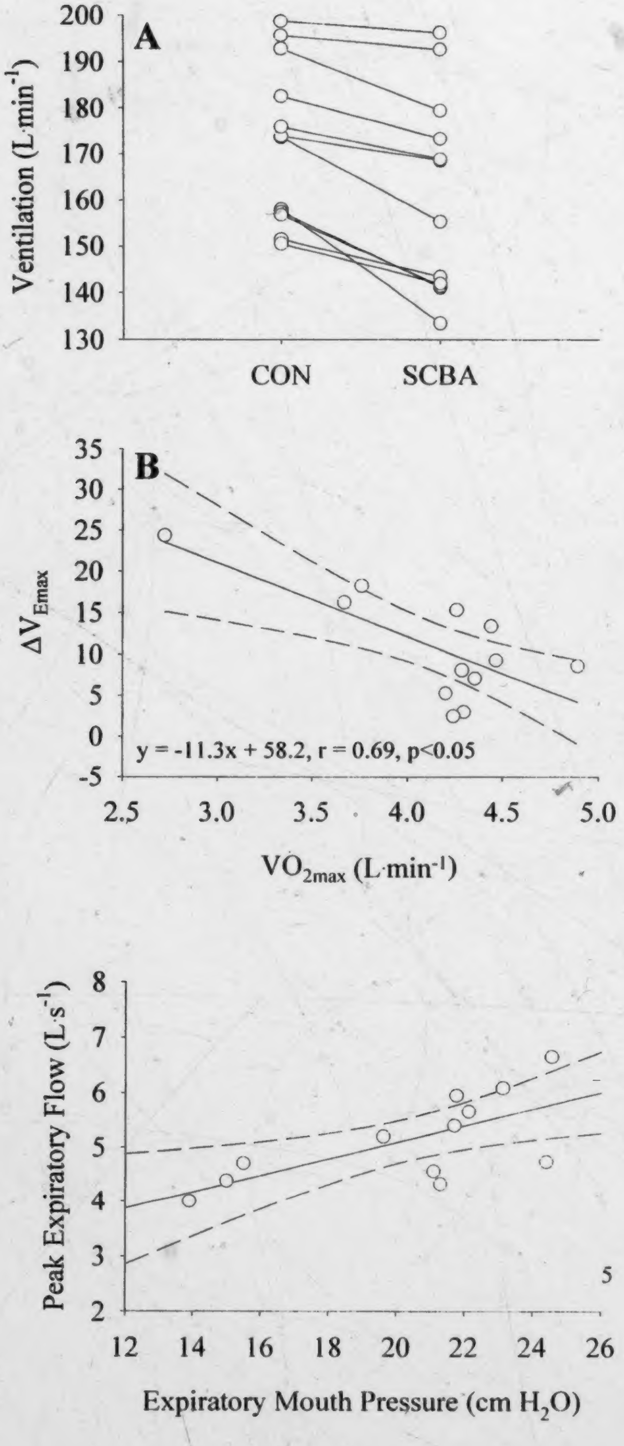

Figure II-4: The individual changes in maximal ventilation between the SCBA and CON trials, * = $p<0.05$; SCBA vs. CON (A). The relationship between the reduction in maximal ventilation (ΔV_{Emax}) with the SCBA and VO_{2max} measured in the control condition (B). The relationship between peak expiratory mouth pressure and expiratory flow rate at maximal exercise with the SCBA (C).

CHAPTER III

Effects of Helium and 40% O_2 on Graded Exercise with Self-Contained Breathing Apparatus.

Introduction

In highly trained athletes ventilation-limitation has been implicated as a possible determinant of maximal exercise performance (Dempsey and Wagner, 1999). In healthy, moderately trained individuals, ventilation (V_E) at peak exercise is considered sufficient for exercise demand and other pulmonary, cardiovascular and metabolic limitations are considered more important in governing maximal work capacity (Jones and Killian, 2000). However, while wearing a self-contained breathing apparatus (SCBA), ventilation-limitation during exercise has been reported even in untrained individuals (Louhevaara et al., 1985, Eves et al., 2000). This SCBA-induced constraint to V_E is due to the added external resistance to expiration and can limit maximal exercise performance (Eves et al., 2000).

Helium-oxygen mixtures have previously been employed to determine the extent that expiratory airflow limitation (Babb et al., 1991) and inadequate ventilation (Buono and Maly, 1996) limit maximal exercise performance. Helium has a lower density than nitrogen and thus maintains laminar flow at higher flow rates, which in turn, decreases both flow resistance and the muscular effort required to exhale (Brice and Welch, 1983).

A version of this chapter is published in the Canadian Journal of Applied Physiology

Reference: Eves, N.D., Petersen, S.R. and Jones, R.L. (2003). Effects of helium and 40% O_2 on graded exercise with self-contained breathing apparatus. Can. J. Appl. Physiol 28(6): 910-926.

The resistive unloading with helium has been reported to increase ventilatory rates during heavy exercise in athletes (Buono and Maly, 1996) and sedentary individuals (Esposito and Ferretti, 1997; Hussain et al., 1985). In a number of studies (Brice and Welch, 1983; Powers et al., 1986), VO_{2max} increased in conjunction with the enhanced V_E, demonstrating that the respiratory system can limit maximal exercise performance in healthy individuals during normal mouth breathing. Due to the higher expiratory breathing resistance, the SCBA regulator should cause greater turbulence to airflow than mouth breathing. In theory, helium-based gas could reduce the muscular effort needed to breathe, reduce any ventilatory limitation imposed by the SCBA and enhance VO_{2max}.

In a previous exercise study with the SCBA, we demonstrated that hyperoxia (HOX: 40% O_2, 60% N_2) increased VO_{2max} and maximal power output by 10% (Eves et al., 2002a). However, at VO_{2max} when breathing hyperoxia, V_E and expiratory mouth pressures were similar to those obtained while breathing compressed air, indicating that the external breathing resistance may still limit maximal exercise performance with hyperoxia. To date we are unaware of any studies that have investigated the effect of combining helium and hyperoxia on exercise capacity with the SCBA. We hypothesized that hyperoxic-helium would have a greater effect on maximal exercise performance than helium or hyperoxia alone. Therefore, the purpose of this study was to investigate the effects of reduced gas density and increased inspired oxygen content on graded exercise with the SCBA.

Methods

Participants

Fifteen healthy, active males with normal pulmonary function provided written informed consent to participate in the study, which had received institutional ethics review board approval. Each participant had previously completed similar graded exercise protocols while dressed in protective clothing and breathing from the SCBA. The physical and pulmonary function characteristics of participants are presented in Table III-1.

Experimental Protocol

During a two-week period, each participant completed a standard spirometry test (SensorMedics 2450, Yorba Linda, CA) to assess lung function and maximal voluntary ventilation (MVV) and then four maximal graded exercise tests (GXT) while dressed in firefighting gear and breathing from the SCBA. The first GXT was always with normoxia (NOX: 21% O_2, 79% N_2). We have previously shown that with well-motivated individuals who are experienced with maximal exercise testing VO_{2max} is highly reproducible, independent of test order (Eves et al., 2002a). The GXT with NOX was followed by randomly assigned tests where participants breathed hyperoxia (HOX: 40% O_2, 60% N_2), helium-oxygen (HE-OX: 21% O_2, 79% He) or helium-hyperoxia (HE-HOX: 40% O_2, 60% He). Participants were blinded to the gas mixture used and were requested to avoid making any vocal sounds while breathing from the SCBA and for approximately three minutes after each test, due to the change in voice pitch with helium. All tests were performed at a similar time of day and separated by at least 48 hours.

Participants refrained from additional strenuous exercise while in the study and prepared for each test in a consistent fashion.

The inspired gas was delivered through the SCBA regulator from unlabelled K-cylinders located beside the treadmill. The gas in each tank was prepared according to medical gas standards and had been chemically analyzed in the manufacturer's laboratory (Praxair Canada Inc., Edmonton, AB).

To simulate some of the stresses of firefighting, participants dressed in firehouse clothing (Firewear^{TM} shirt and trousers) and in National Fire Protection Association standard 1500 compliant protective clothing. A Scott 4.5 bottle and backpack were carried to provide the weight and thoracic constraint normally associated with the SCBA. The mean weight of the SCBA and protective clothing was 22.1 ± 0.3 kg. Two compromises to 'full protective equipment' were made in order to facilitate data acquisition. For safety and comfort during maximal exercise, running shoes were worn instead of firefighting boots. Only one glove was worn to allow measurement of oxyhemoglobin saturation with pulse oximetery (SensorMedics, Yorba Linda, CA), which has been previously validated during exercise (Mengelkoch et al., 1994). Heart rate was continuously monitored using telemetry (Polar Beat, Polar Electro, Lachine, PQ).

Self-Contained Breathing Apparatus

The Scott 4.5 SCBA was used in this investigation (Scott Health and Safety, Monroe, NC). This particular model of SCBA is currently in use by many fire departments and is representative of modern SCBA technology. The SCBA consisted of a light-weight Kevlar® cylinder and valve assembly; a harness and backframe; an automatic dual path redundant pressure-reducing regulator; a full face piece assembly and a removable, facepiece-mounted positive-pressure breathing regulator (SCOTT PRESUR-PAK®, E-Z FLO™) with a purge valve. Inactivation of the air-saver switch and low-pressure alarms were the only changes made to the experimental SCBA over those used in the field. The purge valve was closed during all experiments. All of the SCBA components used in this research were maintained within the manufacturer's specifications by a qualified Scott technician.

Gas Exchange Measurements

Expired gases were collected for measurement of V_E and oxygen consumption (VO_2). The experimental set-up used has been described previously (Eves et al., 2002a). Briefly, a plexiglass cone was designed to fit over the exhalation ports of the SCBA regulator to duct expired gas to the mixing chamber of a TrueMax (Parvo, Salt Lake City, UT) metabolic measurement system. The gas analyzers were calibrated before each test and verified immediately after using primary standard gases containing appropriate concentrations of O_2 and CO_2 in either N_2 or He.

Ventilatory parameters (V_E, tidal volume, breathing frequency, and inspiratory and expiratory time) were measured using a pneumotachometer (Hans Rudolph, Kansas City, MO) calibrated with the appropriate inspired gas for each GXT. This was achieved by connecting the inspired side of a two-way breathing valve (Hans Rudolph, Kansas City, MO) to a reservoir bag filled with the inhaled gas mixture. The expired side of the valve was connected to the metabolic measurement system and, using a calibration syringe, flow rates between 60 L·min^{-1} and 600 L·min^{-1} were generated and a standard curve was constructed. Following this procedure, and just prior to the GXT, the pneumotachometer calibration was confirmed using the inhaled gas mixture and the same range of flows as for construction of the standard curve. Calibrations were always within 1% of the previously constructed standard curve for the gas mixture used.

The accuracy of the TrueMax analyzers in measuring VO_2 with helium-based gas mixtures has been evaluated in our laboratory. In these pilot experiments, nitrogen or helium based gas mixtures containing differing oxygen fractions were passed through the analyzers at selected ventilation rates to produce a range of oxygen consumptions. Regression analysis of the measurements of oxygen consumption with helium and nitrogen gas mixtures demonstrated that the metabolic measurement system used in this experiment accurately measured $\dot{V}O_2$ regardless of the inert gas. Furthermore, the VO_2 values were highly reproducible ($r^2 = 0.99$).

Pulmonary Function Tests

Before performing the graded exercise tests, participants underwent a standard spirometry test to ascertain pulmonary function. All tests were performed in the sitting position using a computerized spirometry system (SensorMedics 2450). Measurements of forced vital capacity (FVC) and forced expired volume in one second (FEV_1) were made according to the recommendations of the American Thoracic Society (1995). Subjects performed a minimum of three FVC maneuvers to ensure a good reproducibility of data and the highest values for FVC and FEV_1 were accepted. Maximum voluntary ventilation was also measured using the same spirometry system. Each participant was encouraged to maintain a maximal effort, breathing as quickly and as deeply as possible over a 12-second period. After a brief rest the test was repeated. The highest value was accepted as the MVV. Normative values were obtained from those reported by Morris et al., (1976).

Maximal Voluntary Ventilation with the SCBA

Maximal voluntary ventilation was measured immediately before each GXT while breathing the test gas mixture from the SCBA. The participant was encouraged to maintain a maximal effort while breathing as fast and as deep as possible over a 10-second period. Expired gases were collected in a Tissot spirometer (Collins, Braintree, MA) and volumes were corrected to body temperature and pressure saturated with water vapor (BTPS).

Graded Exercise Protocol

Each participant followed the same protocol for all four test days. They warmed up for five minutes at an individually selected test speed (3.5 or 4 mph) on a level treadmill. The warm-up also acted as a wash-in period for the test gas mixture. The participant continued to walk at the selected speed and the test began with a 2% increase in grade. Thereafter, the grade was increased 2% every two minutes until ventilatory threshold (VT) was detected by a systematic increase in the V_E/VO_2 ratio, while V_E/VCO_2 remained constant or declined slightly (Wasserman, 1987). The grade was then increased by 2% every minute until exhaustion. The highest 20 second VO_2 value was accepted as VO_{2max} if at least two of the following criteria were met: a plateau in oxygen consumption with an increase in grade; a RER >1.10 and/or attainment of predicted or previously measured maximum heart rate. Maximal power output was then calculated using the following equation [mass x speed x grade].

Peak inspiratory and expiratory mask pressures were measured at the end of each workload and at maximal exercise using a 0.5 cm inside diameter tube connecting the mask and a differential pressure transducer (MP45, Validyne, Northridge, CA). Mask pressure was recorded on a high-speed chart recorder (Gould, Cleveland, OH). The reported peak inspiratory and expiratory pressures were the mean of five consecutive ventilatory cycles. Mean expiratory flow was calculated (tidal volume/ expiratory time) and then used to estimate external breathing resistance during expiration (expiratory mask pressure/ mean expiratory flow).

Ratings of perceived exertion (RPE) were recorded at the end of each stage using the Borg 15 point scale (Borg, 1982). Perceptions of respiratory distress (PRD) were also measured using a modified version of the 7-point psychophysical scale previously described (Morgan and Raven, 1985) where odd numbers rated as follows: 1 = "I am not aware of my breathing"; 3 = "I am starting to breathe harder"; 5 = "It is becoming harder to breathe" and 7 = "I am not getting enough air".

Additional Graded Exercise Test.

To evaluate the effect of the SCBA and protective equipment on VO_{2max} compared to a regular graded exercise test an additional GXT was administered to 8 of the 15 subjects within one week of completing the study. For this test, subjects were dressed in shorts and T-shirt and breathed room air through a Hans-Rudolph two-way breathing valve (Hans Rudolph, Kansas City, MO). The same protocol and criteria for achieving VO_{2max} reported above were used for this test.

Statistical Analysis

All dependent variables measured at maximal exercise and ventilatory threshold with the experimental gas mixtures (HOX, HE-OX and HE-HOX) and the control gas (NOX), were analysed with a repeated-measures ANOVA. When the ANOVA detected a significant effect, post-hoc comparisons were performed with the Scheffe post hoc multiple comparisons test. Additionally, a repeated measures ANOVA was also used to assess the tidal volume and breathing frequency responses with the four gas mixtures at comparable ventilation rates. For all analysis of variance and the post hoc tests the alpha level was set *a priori* at 0.05.

To ascertain any association between the exhaled gas density and any changes in maximal voluntary ventilation and maximal ventilation with the SCBA, simple regression analysis using Pearson correlations was performed.

Results

The main aim of this study was to investigate the effects of HOX, HE-OX and HE-HOX on maximal exercise performance with the SCBA compared to the standard practice of breathing compressed air. Therefore, the majority of results reported within this section will focus on the comparisons between the three experimental gases and NOX. It is also possible to compare differences between all four-gas mixtures. These findings are not discussed in detail to avoid unnecessary complexity. However, significant differences between all four gas mixtures are reported in Tables III-2 to III-4.

Maximal Exercise Results

All maximal exercise results are presented in Table III-2. Compared to NOX, VO_{2max} was significantly increased with HOX (12.9 ± 5.6%), HE-OX (10.2 ± 6.3%) and HE-HOX (21.8 ± 5.6%). The increase in VO_{2max} with HE-HOX was significantly greater than any other condition. Power output at maximal exercise was also increased 9.2 ± 8.9% with HOX and 11.3 ± 8.3% with HE-HOX but was unchanged with HE-OX. Concomitant with the increase in VO_{2max}, VCO_2 was also increased with HOX, HE-OX and HE-HOX. Oxyhemoglobin saturation at maximal exercise was significantly lower than resting values with all gas mixtures. However, at VO_{2max}, oxyhemoglobin saturation was significantly higher than NOX with HOX, and both helium gases. No significant difference was found for RPE between the four gas mixtures, which indicate that subjects perceived the effort given in each test to be similar at peak exercise, despite the large increases in VO_{2max} for all three experimental gases.

The breathing patterns during exercise are shown in Figure III-1. At ventilations below 100 $L \cdot min^{-1}$, there was no significant difference between the four gas mixtures. However, at comparable ventilation rates above 100 $L \cdot min^{-1}$, the two helium-based gases resulted in higher tidal volumes and lower breathing frequencies compared to the nitrogen-based mixtures. At peak exercise, the higher ventilation rates observed with the helium mixtures were associated with significantly higher tidal volumes and breathing frequencies (Table III-2).

Maximum voluntary ventilation on the SCBA was significantly greater with HE-OX (225 ± 37 $L \cdot min^{-1}$) and HE-HOX (207 ± 26 $L \cdot min^{-1}$) compared to NOX (175 ± 27 $L \cdot min^{-1}$) and HOX (172 ± 29 $L \cdot min^{-1}$). However, due to the significant increase in V_E with the helium gases, V_E/MVV at maximal exercise on the SCBA was unaffected by the gas mixture and ranged from 84-90% of the SCBA MVV (Table III-2). At maximal exercise, inspiratory times were not affected by gas mixture but expiratory times were decreased and mean expiratory flow was increased with both HE-OX and HE-HOX.

Peak inspiratory and expiratory mask pressures were lower with the helium mixtures but not with HOX. As a result of the decreased expiratory pressure and the increase in mean expiratory flow with the helium mixtures, external breathing resistance during expiration was 47.6 ± 7.6% and 32.9 ± 8.9% lower with HE-OX and HE-HOX, respectively. In addition to increased flow rates, decreased mask pressures and decreased external breathing resistance, PRD was also significantly reduced at maximal exercise with HE-HOX.

Comparison of Results at Ventilatory Threshold

Results at VT for each gas mixture are reported in Table III-3. Ventilatory threshold occurred at a significantly higher VO_2 with HOX and HE-HOX but not with HE-OX. Compared to the normoxic VO_{2max}, VT occurred at a significantly higher percentage of VO_{2max} with the two hyperoxic mixtures. Moreover, VT occurred at a higher percentage of normoxic VO_{2max} with HE-HOX than all other gases. To accompany the increase in VO_2 at VT, power output was also higher with HOX (9.8 ± 5.0%) and HE-HOX (14.6 ± 5.8%). The respiratory exchange ratio, heart rate and RPE were similar between all four gas mixtures and as expected oxyhemoglobin saturation was significantly higher with the hyperoxic gases.

Minute ventilation at VT was significantly higher with HE-HOX but not HOX despite the similar increases in power output achieved. The increase in V_E with HE-HOX was due to a significant higher breathing frequency. At ventilatory threshold, mean expiratory flow was increased and inspiratory and expiratory mask pressures were reduced with HE-OX and HE-HOX. The increase in mean expiratory flow and the reduction in peak expiratory pressure with the helium based gases resulted in a reduction in external breathing resistance of 24.8 ± 16.3 % with HE-OX and 24.6 ± 12.6 % with HE-HOX. Perceived respiratory distress was not significantly different with any gas mixture.

Comparison of Responses at the Normoxic Ventilatory Threshold

Table III-4 shows a comparison of selected physiological parameters at a comparable power output to where VT occurred with NOX. At this workload, no significant difference was found in VO_2 between the four gas mixtures. RER was significantly reduced with HOX and HE-HOX but unchanged with HE-OX. Compared to NOX, heart rate was significantly lower and arterial saturation significantly higher with HOX and HE-HOX, while no differences were found for either variable with HE-OX. At this comparable power output the rating of perceived exertion was not different from NOX with HOX and HE-OX but was lower with HE-HOX.

Ventilation was similar between NOX and the two helium mixtures at this power output but it was lower with HOX. The lower V_E with HOX was due to a reduction in tidal volume without a change in breathing frequency. Inspiratory mask pressure was significantly lower with HE-OX and expiratory mask pressure was decreased with all three experimental gases. Furthermore, expiratory flow was enhanced and external breathing resistance reduced with the helium gases. However, no significant change in perceived respiratory distress was observed.

Discussion

The primary finding of this study was that all three experimental gas mixtures increased VO_{2max} compared to NOX. The use of helium-based gas mixtures with the SCBA is unique, and both HE-OX and HE-HOX increased V_E above the maximal value obtained with NOX. The extent to which HE-OX enhanced V_E is consistent with other research (Babb, 2001; Buono and Maly, 1996; Esposito and Ferretti, 1997; Krishnan et al., 1997) and combined with a concomitant increase in VO_{2max}, supports the conclusion that pulmonary ventilation is a limiting factor to maximal exercise with the SCBA (Louhevaara et al., 1985, Eves et al., 2000).

Babb (2001) stated that while respiratory drive remains unaltered during heavy exercise with NOX or HE-OX, it is the reduced impedance to airflow with HE-OX that increases V_E. This is the most plausible explanation for the increased V_E in the present study. Gas flow through the regulator and the respiratory airways is either laminar or turbulent depending on airway radius, velocity of flow, and the viscosity and density of the gas mixture. As helium has a density seven times lower and a viscosity only slightly higher than nitrogen, flow during helium breathing becomes turbulent or transitional at significantly higher flow rates than with air. This would decrease the resistance to gas flow through the SCBA regulator and subsequently would reduce the expiratory flow limitation imposed by the SCBA, allowing V_E to increase. There were high correlations between exhaled gas density and MVV (r=0.99) and V_E at maximal exercise (r=0.99) confirming that the ventilatory effects of the experimental gases used in our study were due to the physical properties of the gases (Figure III-2).

At normoxic VT, the ventilatory response to exercise for HE-OX and HE-HOX was not significantly different from NOX. This finding demonstrates that at lower ventilatory volumes where flow may still be predominantly laminar V_E is not dependent on gas density, which agrees with others (Babb, 1997; Babb, 2001; Brice and Welch, 1983). However, at VO_{2max} ventilation was increased with HE-OX and HE-HOX as previously mentioned, which confirms the benefits of resistive unloading with helium are greater at higher ventilatory outputs where turbulent flow would be more predominant. In contrast to the helium mixtures, V_E was lower with HOX at the normoxic VT. This finding supports previous work that has reported a reduced V_E at submaximal power outputs when fraction of inspired oxygen is increased (Eves et al., 2002b; Byrnes and Mullin, 1981; Wilson and Welch, 1975) and is likely due to a direct reduction of peripheral chemoreceptor activation (O'Donnell et al., 2001).

The breathing patterns shown in Figure 1, where tidal volume reached a plateau, have been reported for endurance-trained athletes accompanying flow limitation and when end-inspired lung volume exceeds 85% of TLC (McClaran et al., 1999). At high lung volumes, the elastic work of breathing is elevated and forces further increases in V_E to be driven by breathing frequency alone. Our finding of a plateau in tidal volume at relatively lower ventilation rates with the nitrogen-based mixtures is consistent with an increase in end-expired lung volume (dynamic hyperinflation) with the more dense gas mixtures, which would limit any further tidal volume expansion. Unfortunately, due to the nature of the SCBA, lung volumes could not be determined during exercise in this study. However, as helium reduces expiratory flow limitation, breathing helium-based gases may slow development of any dynamic hyperinflation brought on by the increased expired resistance of the SCBA, thus permitting larger tidal volumes.

Brice and Welch, (1983) correctly point out that a lower ventilatory mass is moved while breathing HE-OX compared to NOX, which implies a reduction in ventilatory effort. In contrast, Babb (2001) reported that breathing HE-OX does not reduce the work of breathing or the peak expiratory pressure at VT or VO_{2max} in healthy elderly subjects with normal pulmonary function. However, Babb (2001) matched the external resistance (valve, pneumotachograph and tubing) between HE-OX and room air to study the work of breathing imposed exclusively by the lung. As we were using HE-OX to decrease the external breathing resistance imposed by the expiratory valves of the SCBA regulator, this was not done. In our study, external expiratory resistance, inspiratory and expiratory mask pressures and PRD were all reduced at VO_{2max} while breathing the helium mixtures suggesting that the SCBA-induced work of breathing was decreased at peak exercise. However, it is possible that the total work of breathing could have been increased since V_E and tidal volume were increased at maximal exercise with the helium mixtures.

Our finding of a 10.2% increase in VO_{2max} with HE-OX was higher than the 6.7% (Powers et al., 1986) and the 5.0% (Brice and Welch, 1983) previously reported. This difference likely reflects the greater benefit of breathing helium when there is an added external resistance such as the SCBA. The 21.8% increase in VO_{2max} with HE-HOX was substantially greater than that obtained with HE-OX or HOX. As this is the first report of VO_{2max} measured during hyperoxic-helium breathing we cannot compare our findings to those of others. The only other study that used hyperoxic-helium during heavy exercise, but not with the SCBA, (Wilson and Welch, 1980) reported that 80% O_2, 20% He increased time to exhaustion approximately 14% over that obtained with hyperoxia (80% O_2, 20% N_2). The results of our study and those of Wilson and Welch (1980) suggest that helium-hyperoxic mixtures have considerably more impact than normoxic-helium or hyperoxia alone. Figure III-3 shows a summary of the VO_{2max} results obtained relative to the gas density of the exhaled gas (assuming the exhaled gas contained 5% CO_2 and a difference between inspired and expired O_2 of 5%). It is interesting that the effect of lowering exhaled gas density has a similar effect on VO_{2max} (similar slopes) regardless of whether the inspired gas contained normoxic or hyperoxic gas. The figure also illustrates that the impact of increasing inspired O_2 is greater than that of decreasing gas density with helium.

The elevated oxyhemoglobin saturation at maximal exercise with all three experimental gas mixtures reflects increased oxygen supply to the working muscles, which in turn would help to increase VO_{2max}. The higher oxyhemoglobin saturation at end-exercise with HE-OX was probably related to the higher V_E (Powers et al., 1986) and supports the hypothesis that V_E is attenuated during heavy exercise while breathing compressed air through the SCBA. In a previous study, we concluded that the increase in VO_{2max} while breathing 40% O_2 from the SCBA, can be explained by increased O_2 delivery secondary to increased oxyhemoglobin saturation (Eves et al., 2002a). The comparable findings in this study support our contention that O_2 supply is predominantly responsible for the increase in VO_{2max} found with HOX.

Figure III-4 illustrates that VO_{2max} increases with higher oxyhemoglobin saturation at maximal exercise. The triangular area bounded by NOX and HOX shows that the effects of oxyhemoglobin saturation on VO_{2max} with the SCBA. However, the effect of helium appears to be over and above the effect of oxyhemoglobin saturation. Furthermore, the effect of HE-HOX combines both the effects of the hyperoxia and helium. This additional effect of helium may be related to unloading of the respiratory musculature during heavy exercise, enhancing O_2 delivery to the other working muscles beyond that simply related to increasing oxyhemoglobin saturation. This is supported by studies that demonstrated respiratory unloading at VO_{2max} with a proportional assist ventilator reduces the demand for O_2 by the respiratory muscles, increases leg blood flow (Harms et al., 1997) and increases maximal power output (Harms et al., 1998).

It is also possible that the external expiratory breathing resistance imposed by the SCBA creates a condition analogous to a "symptom-limited" maximal exercise capacity. The contention that the SCBA limits maximal exercise is supported by the results of the additional GXT administered to 8 of the 15 participants. When compared to the NOX test with the SCBA, VO_{2max} was increased 22.7 ± 2.6%, underscoring the limitations to maximal exercise imposed by the SCBA and the protective clothing. The increases in VO_{2max} with HOX and HE-OX at least partially alleviate these limitations, whereas HE-HOX restores performance to the "normal" level that would be achieved without the SCBA.

We are unaware of any other reports of the assessment of ventilatory threshold with the SCBA. The ventilatory responses normally associated with graded exercise and the concept of an "anaerobic threshold" occur in a very similar fashion compared to those previously reported with mouth breathing (Wasserman, 1987). Furthermore, as VO_2 and V_E were the same for all four gas mixtures at the normoxic VT and the effect of the external breathing resistance imposed by the SCBA appears to only influence V_E at ventilations greater than 100 $L \cdot min^{-1}$, we believe that the ventilatory threshold technique used is appropriate for evaluating exercise responses with the SCBA.

Breathing HE-OX did not change the functional parameters associated with VT (e.g., V_E, VO_2, power output, RPE and HR), however the markers of respiratory effort (e.g., expired flow, inspiratory and expiratory pressure and external breathing resistance) were significantly lower. The two hyperoxic mixtures clearly enhanced the power output at which VT occurred, and this finding has significant implications for work performance with the SCBA. The elevated VT with both HOX and HE-HOX indicates that a higher power output can be achieved before the onset of VT.

At the power output that elicited VT with compressed air, we observed that RER, heart rate and expiratory mask pressure were lower with both hyperoxic mixtures. In addition, external breathing resistance and RPE were lower with HE-HOX. These findings suggest that at submaximal work intensities, breathing a hyperoxic mixture, especially with helium as the inert gas, could improve exercise tolerance in occupations where wearing SCBA is mandatory.

Summary

In summary, HOX, HE-OX and HE-HOX increased VO_{2max} while wearing firefighting gear and breathing from the SCBA. With the hyperoxic mixtures, the increase in aerobic power was associated with an increase in the maximal power output. Normoxic and hyperoxic-helium mixtures increased maximal V_E because of a reduction in the impedance to gas flow through the SCBA regulator. This was associated with increased flow rates, decreased inspiratory and expiratory mask pressure and reduced external breathing resistance both at VT and VO_{2max}. The results of this study clearly demonstrate the ability of normoxic-helium and hyperoxic-helium to decrease expiratory breathing resistance and improve work performance on the SCBA. Furthermore, the ability of HE-HOX to increase VO_{2max} to the same level as breathing room air without the SCBA indicates that this gas mixture can eliminate the restrictions imposed by the SCBA and protective clothing.

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Table III-1: Physical and Pulmonary Function Characteristics

Age (yr)	Mass (kg)	Height (cm)	FEV_1 (%pred)	FEV_1/FVC (%pred)	MVV (%pred)
34 ± 10	77 ± 7	179 ± 5	108 ± 13	104 ± 6	103 ± 17

Values are means ± SD, n=15. *Abbreviations:* FEV_1 = forced expired volume in 1 second, FEV_1/FVC = ratio of FEV_1 to forced vital capacity, MVV = maximum voluntary ventilation obtained during a standard pulmonary function test without the SCBA.

Table III-2: Maximal Exercise Responses.

	NOX (a)	HOX (b)	HE-OX (c)	HE-HOX (d)
VO_2, $Lmin^{-1}$	3.45 ± 0.37^{bcd}	3.90 ± 0.45^{ad}	3.80 ± 0.35^{ad}	4.21 ± 0.49^{abc}
Power Output, W	268 ± 41^{bd}	295 ± 30^{ac}	272 ± 32^{bd}	302 ± 40^{ac}
VCO_2, $L{\cdot}min^{-1}$	4.20 ± 0.43^{bcd}	4.48 ± 0.53^{acd}	4.79 ± 0.44^{abd}	5.02 ± 0.53^{abc}
RER	1.22 ± 0.05^{bc}	1.18 ± 0.05^{ac}	1.27 ± 0.05^{abd}	1.21 ± 0.04^{c}
H_R, $beats{\cdot}min^{-1}$	189 ± 9^{d}	188 ± 9^{d}	189 ± 8^{d}	192 ± 7^{abc}
S_pO_2, %	90.6 ± 2.3^{bcd}	97.1 ± 1.6^{ac}	92.4 ± 2.2^{abd}	97.2 ± 0.8^{ac}
RPE	19.1 ± 0.6	19.1 ± 0.9	18.9 ± 0.8	19.0 ± 0.8
V_E, $L{\cdot}min^{-1}$	148.0 ± 17.3^{cd}	152.0 ± 14.3^{cd}	185.3 ± 21.9^{ab}	179.9 ± 17.31^{ab}
Tidal Volume, L	2.49 ± 0.31^{cd}	2.55 ± 0.40^{cd}	2.81 ± 0.46^{ab}	2.78 ± 0.41^{ab}
f, $breaths{\cdot}min^{-1}$	60.3 ± 10.1^{cd}	60.7 ± 10.0^{cd}	67.5 ± 12.5^{ab}	65.5 ± 10.1^{ab}
V_E /MVV, %	86 ± 12	90 ± 10	84 ± 17	88 ± 11
T_I, s	0.30 ± 0.08	0.29 ± 0.08	0.33 ± 0.07	0.29 ± 0.06
T_E, s	0.72 ± 0.12^{cd}	0.72 ± 0.11^{cd}	0.59 ± 0.11^{abd}	0.65 ± 0.11^{abc}
V_T/T_E, $L{\cdot}s^{-1}$	3.50 ± 0.41^{cd}	3.56 ± 0.34^{cd}	4.81 ± 0.64^{abd}	4.35 ± 0.45^{abc}
P_I, cm H_2O	-4.4 ± 1.2^{cd}	-4.3 ± 1.3^{cd}	-2.1 ± 0.6^{abd}	-3.4 ± 1.2^{abc}
P_E, cm H_2O	22.8 ± 3.9^{cd}	22.5 ± 3.5^{cd}	16.2 ± 2.6^{abd}	18.9 ± 3.5^{abc}
BR, cm $H_2O{\cdot}L^{-1}{\cdot}s^{-1}$	6.5 ± 0.8^{cd}	6.3 ± 0.7^{cd}	3.4 ± 0.3^{abd}	4.3 ± 0.6^{abc}
PRD	5.7 ± 0.7^{d}	5.2 ± 1.1	5.1 ± 1.1	4.9 ± 1.0^{a}

Values are means ± SD. *Abbreviations:* VO_2 = oxygen consumption, VCO_2 = carbon dioxide produced, RER = respiratory exchange ratio, H_R = heart rate, S_pO_2 = oxyhemoglobin saturation, RPE = rating of perceived exertion, V_E = ventilation, f = breathing frequency, V_E/MVV = ratio of maximal V_E to MVV, T_I = inspiratory time, T_E = expiratory time, V_T/T_E = mean expiratory flow, P_I = inspired mask pressure, P_E = expired mask pressure, BR = external breathing resistance during expiration, PRD = perceived respiratory distress. [a] = different from NOX, $p<0.05$; [b] = different from HOX, $p<0.05$; [c] = different from HE-OX, $p<0.05$; [d] = different from HE-HOX, $p<0.05$.

Table III-3: Responses at Ventilatory Threshold for each Gas Mixture.

	NOX (a)	HOX (b)	HE-OX (c)	HE-HOX (d)
VO_2, L·.min^{-1}	2.20 ± 0.30^{bd}	2.53 ± 0.37^{ac}	2.26 ± 0.32^{bd}	2.69 ± 0.36^{ac}
VT, %	64 ± 8^{bd}	74 ± 9^{acd}	66 ± 7^{bd}	78 ± 9^{abc}
Power Output, W	114 ± 29^{bd}	136 ± 33^{ac}	115 ± 26^{bd}	135 ± 32^{ac}
RER	0.94 ± 0.03	0.93 ± 0.02	0.94 ± 0.05	0.93 ± 0.04
H_R, beats·min^{-1}	157 ± 12	155 ± 15	154 ± 15	159 ± 12
S_pO_2, %	93 ± 1^{bd}	98 ± 0.7^{ac}	94 ± 1.4^{bd}	98 ± 0.8^{ac}
RPE	12.7 ± 1.6	13.1 ± 1.2^{c}	12.3 ± 1.3^{b}	12.9 ± 1.5
V_E, L·min^{-1}	63.6 ± 10.1^{d}	66.7 ± 10.1^{d}	65.3 ± 11.2^{d}	73.2 ± 10.7^{abc}
Tidal Volume, L	2.17 ± 0.52	2.12 ± 0.45	2.06 ± 0.41	2.22 ± 0.44
f, Breaths·min^{-1}	30 ± 6^{d}	33 ± 7	33 ± 8	34 ± 7^{a}
V_T/T_E, L·s^{-1}	1.72 ± 0.30^{cd}	1.79 ± 0.30^{d}	1.90 ± 0.41^{a}	2.01 ± 0.35^{ab}
P_I, cm H_2O	-1.5 ± 0.9^{cd}	-1.4 ± 0.4^{c}	-0.8 ± 0.4^{ab}	-1.05 ± 0.3^{a}
P_E, cm H_2O	10.0 ± 1.8^{cd}	9.7 ± 1.9^{cd}	8.1 ± 1.5^{ab}	8.7 ± 1.4^{ab}
BR, cm $H_2O \cdot L^{-1} \cdot s^{-1}$	5.9 ± 1.0^{cd}	5.4 ± 1.0^{cd}	4.4 ± 1.2^{ab}	4.4 ± 0.8^{ab}
PRD	2.9 ± 0.7	2.9 ± 1.1	2.4 ± 0.5	2.7 ± 0.9

Values are means ± SD. *Abbreviations:* VO_2 = oxygen consumption, VT = ventilatory threshold as a percentage of normoxic VO_{2max}, RER = respiratory exchange ratio, H_R = heart rate, S_pO_2 = oxyhemoglobin saturation, RPE = rating of perceived exertion, V_E = ventilation, f = breathing frequency, V_T/T_E = mean expiratory flow, P_I = inspired mask pressure, P_E = expired mask pressure, BR = external breathing resistance during expiration, PRD = perceived respiratory distress. [a] = different from NOX, $p<0.05$; [b] = different from HOX, $p<0.05$; [c] = different from HE-OX, $p<0.05$, [d] = different from HE-HOX, $p<0.05$.

Table III-4: Responses at the Normoxic Ventilatory Threshold.

	NOX (a)	HOX (b)	HE-OX (c)	HE-HOX (d)
VO_2, $L \cdot min^{-1}$	2.20 ± 0.30	2.28 ± 0.28	2.26 ± 0.32	2.32 ± 0.29
RER	0.94 ± 0.03[bd]	0.90 ± 0.03[ac]	0.94 ± 0.05[bd]	0.90 ± 0.04[ac]
H_R, beats·min^{-1}	157 ± 12[bd]	149 ± 14[a]	154 ± 15	151 ± 12[a]
S_pO_2, %	93 ± 1[bd]	98 ± 1[ac]	94 ± 1[bd]	98 ± 1[ac]
RPE	12.7 ± 1.6[d]	12.7 ± 1.4[d]	12.3 ± 1.3	12.0 ± 1.4[ab]
V_E, $L \cdot min^{-1}$	63.6 ± 10.1[b]	59.9 ± 10.0[acd]	65.3 ± 11.2[b]	65.0 ± 9.5[b]
Tidal Volume, L	2.17 ± 0.52[b]	1.94 ± 0.39[a]	2.06 ± 0.41	2.11± 0.36
f, Breaths·min^{-1}	30 ± 6	32 ± 7	33 ± 8	32 ± 7
V_T/T_E, $L \cdot s^{-1}$	1.72 ± 0.30[cd]	1.62 ± 0.25[cd]	1.90 ± 0.41[ab]	1.86 ± 0.30[ab]
P_E, cm H_2O	10.0 ± 1.8[bcd]	8.7 ± 1.6[a]	8.1 ± 1.5[a]	8.2 ± 1.2[a]
P_I, cm H_2O	-1.5 ± 0.9[c]	-1.0 ± 0.5	-0.8 ± 0.4[a]	-1.0 ± 0.4
BR, cm $H_2O \cdot L^{-1} \cdot s^{-1}$	5.9 ± 1.0[cd]	6.0 ± 1.1[cd]	4.4 ± 1.2[ab]	4.5 ± 0.6[ab]
PRD	2.9 ± 0.7	2.4 ± 1.1	2.4 ± 0.5	2.4 ± 0.9

Values are means ± SD. *Abbreviations:* VO_2= oxygen consumption, RER = respiratory exchange ratio, H_R = heart rate, S_pO_2 = oxyhemoglobin saturation, RPE = rating of perceived exertion, V_E = ventilation, f = breathing frequency, V_T/T_E = mean expiratory flow, P_E = expired mask pressure, P_I = inspired mask pressure, BR = external breathing resistance during expiration, PRD = perceived respiratory distress. [a] = different from NOX, $p<0.05$; [b] = different from HOX, $p<0.05$; [c] = different from HE-OX, $p<0.05$, [d] = different from HE-HOX, $p<0.05$.

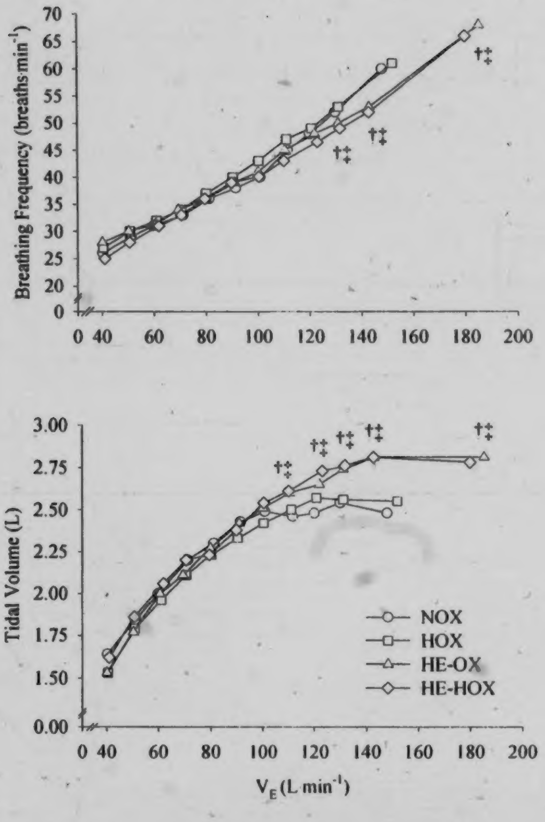

Figure III-1. The relationship between breathing frequency and tidal volume at comparable ventilations (V_E) during graded exercise while breathing the experimental gas mixtures from the SCBA. Comparisons are made between each gas mixture and NOX. As V_E was significantly greater with the helium gas mixtures at end exercise, the final comparison is made between the peak exercise values. n=15. † = HE-OX significantly different from NOX ($p<0.05$). ‡ = HE-HOX significantly different from NOX ($p < 0.05$).

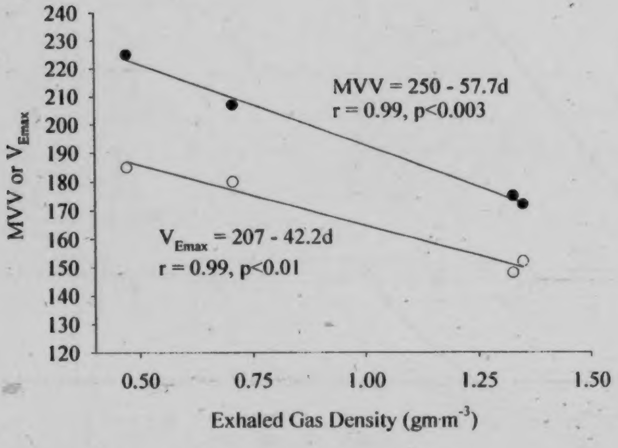

Figure III-2: The relationship between gas density and maximal ventilation (V_E) and the relationship between gas density and maximal voluntary ventilation (MVV). Both V_E and MVV are measured while breathing from the SCBA. d = gas density.

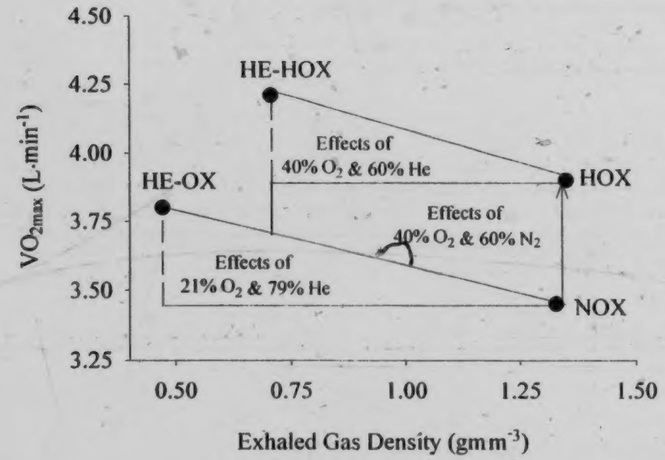

Figure III-3: Relative effects of gas density and fractional of inspired oxygen (F_IO_2) on VO_{2max}.

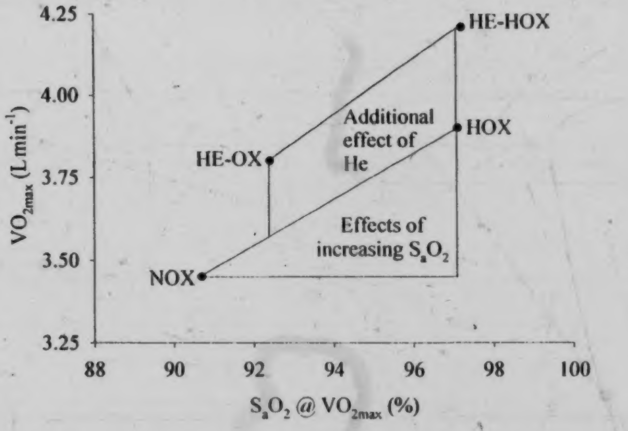

Figure III-4: The effects of oxyhemoglobin saturation (S_aO_2) and helium on VO_{2max}.

CHAPTER IV

Submaximal Exercise with Self-Contained Breathing Apparatus: The Effects of Hyperoxia and Inspired Gas Density.

Introduction

The self-contained breathing apparatus (SCBA) worn by a number of occupational groups to protect the respiratory system from hazardous pollutants adds an external resistance to expiratory flow, which has been shown to limit minute ventilation (V_E) (Louhevaara et al., 1985) and reduce submaximal exercise performance (Louhevaara et al., 1986). Although a number of advances in SCBA technology have been made since these studies, recent work has demonstrated that an expiratory resistance greater than that observed while mouth breathing still exists (Eves et al., 2000). It is therefore of interest to explore ways to reduce the external expiratory breathing resistance and the expiratory work associated with sustained exercise with the SCBA.

The effects of breathing normoxic-helium on exercise performance are well documented in healthy individuals (Brice and Welch, 1983; Esposito and Ferretti 1997; Babb et al., 2003). Due to the higher expiratory resistance, the SCBA regulator should cause greater turbulence to airflow than mouth breathing at the same ventilation. The lower density of helium promotes laminar flow, which in turn, decreases both flow resistance and the muscular effort required to exhale (Brice and Welch, 1983). Decreased

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flow resistance with helium reduces expiratory flow limitation (McClaren et al., 1999) and improves performance during heavy exercise while mouth breathing (Brice and Welch, 1983; Aaron et al., 1985, Powers et al., 1986), but the effects of helium on the expiratory resistance from the SCBA regulator have not been reported.

Through a different mechanism, hyperoxia can also reduce respiratory effort by decreasing V_E at submaximal exercise intensities (Byrnes et al., 1984, O'Donnell et al., 2001), which in turn has been shown to improve exercise tolerance when breathing against a resistance (Dressendorfer et al., 1977). Furthermore, work from our laboratory has demonstrated that hyperoxia decreases inspiratory and expiratory pressures associated with the SCBA (Eves et al., 2002a,b) and decreases time to complete a circuit of simulated firefighting tasks (Petersen et al., 2000).

Only one study has previously investigated the effects of helium-hyperoxia on exercise performance (Wilson and Welch, 1980). These authors demonstrated that during mouth breathing, 80% O_2, 20% He enhanced submaximal exercise capacity above that of normoxic-helium and hyperoxia alone. These findings suggest that the benefits of breathing helium-hyperoxia could be greater than normoxic-helium or hyperoxia. Therefore, the purpose of the present study was to investigate the effects of reduced density gas mixtures and increased inspired oxygen fraction on external breathing resistance during submaximal exercise with the SCBA.

Methods

Subjects

Fifteen moderately to well-trained males with normal pulmonary function volunteered to participate in the study. All subjects were completely accustomed to strenuous exercise with the SCBA and provided written informed consent to participate in the study, which had previously received institutional ethics review board approval. The physical and pulmonary function characteristics of the subjects are presented in Table IV-1.

Experimental Protocol

During a two-week period, each subject completed a spirometry test to assess pulmonary function, a graded exercise test (GXT) and four 30-minute submaximal exercise trials. The 30-minute trials were performed at the speed and grade associated with ventilatory threshold during the GXT. Pilot work had revealed this intensity to be a stressful but tolerable workload for 30 minutes. Additionally, 30 minutes is probably the absolute maximum time a firefighter could expect to work on the SCBA before having to change the air bottle.

The graded exercise test was performed first to determine ventilatory threshold and VO_{2max} while breathing compressed air from the SCBA. Then the four submaximal trials were performed in a random order. The gas mixtures used were compressed air (NOX: 21% O_2, 79% N_2), hyperoxia (HOX: 40% O_2, 60% N_2), normoxic-helium (HE-OX: 21% O_2, 79% He) and helium-hyperoxia (HE-HOX: 40% O_2, 60% He). Gas mixtures were delivered to each subject through the SCBA regulator from cylinders located adjacent to the treadmill. Subjects were blinded to the gas mixture used. To decrease the probability of the test gas mixture being identified, participants were requested to avoid making any vocal sounds when breathing from the SCBA and for three minutes after each test, as helium affects voice pitch. All tests were separated by at least 48 hours, during which time participants refrained from other strenuous exercise. Participants were asked to prepare for each test in a consistent fashion (e.g., diet, hydration, rest).

To simulate some of the stresses of firefighting, subjects dressed in firehouse clothing (Firewear™ shirt and trousers) and in National Fire Protection Association standard 1500 compliant protective clothing for the GXT and the four experimental trials. A Scott 4.5 bottle and backpack were carried to provide the weight and thoracic constraint normally associated with the SCBA. The mean weight of the SCBA and protective clothing was 22.1 ± 0.3kg. Two compromises to 'full protective equipment' were made. For safety and comfort during exercise, running shoes were worn instead of firefighting boots and only one glove was worn to allow blood collection and measurement of oxyhemoglobin saturation with pulse oximetery (Sat-Trak, SensorMedics, Yorba Linda, CA).

Self-Contained Breathing Apparatus

The self-contained breathing apparatus used in this investigation were Scott 4.5 SCBA (Scott Health and Safety, Monroe, NC). This particular model of SCBA is currently in use by many fire departments and is representative of modern SCBA technology. The SCBA consisted of a light-weight Kevlar® cylinder and valve assembly; a harness and backframe; an automatic dual path redundant pressure-reducing regulator; a full face piece assembly and a removable, facepiece-mounted positive-pressure breathing regulator (SCOTT PRESUR-PAK®, E-Z FLO™) with a purge valve. Inactivation of the air-saver switch and low-pressure alarms were the only changes made to the experimental SCBA over those used in the field. The purge valve was closed during all experiments. All of the SCBA components used in this research were maintained within the manufacturer's specifications by a qualified Scott technician.

Pulmonary Function Tests

Before performing the graded exercise tests, subjects underwent a spirometry test to measure pulmonary function. All tests were performed in the sitting position using a computerized spirometry system (SensorMedics 2450). Measurements of forced vital capacity (FVC) and forced expired volume in one second (FEV_1) were made according to the recommendations of the American Thoracic society (ATS, 1995). Each subject performed at least three FVC maneuvers to ensure that the highest values for FVC and FEV_1 were obtained. Maximum voluntary ventilation (MVV) was then measured using the same spirometry system. The test was repeated twice and the highest value was accepted as the MVV. Normative values were obtained from those reported by Morris et al., (1976).

Graded Exercise Protocol

Subjects walked on a motorized treadmill at an individually selected test speed (3.5 or 4.0 mph). Grade increased by 2% every two minutes until ventilatory threshold, which was detected by a systematic increase in the V_E/VO_2 ratio, while V_E/VCO_2

remained constant or declined slightly (Wasserman, 1987). The grade was then increased 2% every minute until exhaustion to obtain VO_{2max}. The highest 20 second VO_2 value was accepted as VO_{2max} if at least two of the following criteria were met: a plateau in oxygen consumption with an increase in grade; a RER >1.10 and/or attainment of predicted or previously measured maximum heart rate.

Experimental Trials

Each trial began with a five-minute warm up (at the same walking speed as in the GXT) on a level treadmill. This also served as a wash-in period for the test gas mixture. After the standardized warm up, grade was increased to where ventilatory threshold occurred during the GXT and subjects continued to exercise for 30-minutes. Throughout each trial, heart rate was continuously monitored using a Polar telemetry system (Polar, USA, Inc., Standford, CT). On completion of each trial, the participant cooled down at 2.5 mph on a flat treadmill for five minutes. The protective clothing was removed and the subject was cooled with a fan and fully re-hydrated before leaving the lab.

Ventilatory Measurements: Ventilatory parameters [V_E, tidal volume (V_T), breathing frequency (f), inspiratory (T_I) and expiratory (T_E) time and mean expiratory flow (V_T/ T_E)] were measured from expired gases using a previously described plexiglass cone (Eves et al., 2002b) and a pneumotachometer (Hans Rudolph, Kansas City, MO) attached to a TrueMax (Parvo, Salt Lake City, UT) metabolic measurement system. Volume calibration was done by connecting the inspired side of a two-way breathing valve (Hans Rudolph, Kansas City, MO) to a reservoir bag filled with the inspired gas mixture. The expired side of the valve was connected to the pneumotachometer which was calibrated using a 3-litre syringe at flow rates between 60 $L \cdot min^{-1}$ and 600 $L \cdot min^{-1}$ to construct a standard curve for each gas mixture. Prior to each test, a volume validation was then performed using the test gas mixture to ensure measured volumes were always within an acceptable range (<1% error) compared to the appropriate standard curve. Total gas consumption was calculated by summing the minute values for V_E. The mean ventilatory mass moved by the lungs was also calculated at five-minute intervals throughout each trial using the product of V_E and the inspired gas density.

Maximal Mouth Pressures: To evaluate the possibility of respiratory muscle fatigue from breathing against the external load of the SCBA regulator, maximal static pressures were measured before each test and immediately after the five minute standardized cool-down. Specifically, maximal inspiratory (MIP) and expiratory (MEP) mouth pressures were measured breathing room air at residual volume and total lung capacity, respectively. The apparatus used was a modified version of that previously described (Black and Hyatt, 1969) and consisted of a tube 9 cm long with a 3 cm inside diameter, which was closed at one end and connected to a pressure transducer (Validyne DP15, Northridge, CA) by a 0.5cm inside diameter tube. A small hole (0.5 mm) was drilled in the closed end of the tube to prevent artificial pressure spikes. The transducer was calibrated to 300 cmH_2O with a mercury manometer prior to each test and the signal was amplified (Validyne CD15, Northridge, CA) and displayed on a chart recorder (Gould 2400S, Cleveland, OH). Subjects repeated each test until values began to decline. The highest values were recorded as MIP and MEP.

Peak Mask Pressures: Peak expiratory mask pressures were measured at 5-minute intervals throughout each trial using a differential pressure transducer (Validyne DP45-28, Northridge, CA). The transducer was connected to the face piece assembly by a 0.5 cm inside diameter tube, attached to a custom-machined metal disc that replaced one of the voice ports on the mask. Mask pressure was recorded on a high-speed chart recorder (Gould, Cleveland, OH). The peak expiratory pressures were calculated using the mean of five consecutive breaths. External expiratory breathing resistance was estimated from expiratory mask pressure and the mean expiratory flow [Breathing resistance = Expiratory Pressure/(V_T/ T_E)]

Blood Lactate Measurements: Before each test, a 20-guage catheter (BD Instyle-W, Sandy, UT) for blood collection was inserted into a distal forearm vein. The catheter was flushed with saline to maintain patency between samples. Prior to drawing the blood sample, the saline was withdrawn and discarded. After the blood sample was drawn with a clean syringe, fresh saline was added. This procedure was repeated for each sample drawn at rest, at 5-minute intervals during each test and at 5 minutes post-exercise. A 200 μL aliquot of venous blood was immediately pipetted into a preservative tube (YSI 2315, Yellow Springs Instruments, Yellow Springs, OH). After vortexing to mix the preservative with the blood, the samples were frozen and subsequently analyzed in duplicate with a blood lactate analyzer (YSI 2300 Stat, Yellow Springs Instruments, Yellow Springs, OH).

Psychophysical Measurement: Psychophysical measurements were recorded at five-minute intervals during each trial. Ratings of perceived exertion (RPE) were measured using the Borg scale (Borg, 1982). Perceived respiratory distress (PRD) was measured using a modified version of the 7-point psychophysical scale described previously (Morgan and Raven, 1985), where odd numbers rated as follows: 1 = "I am not aware of my breathing"; 3 = "I am starting to breathe harder"; 5 = "It is becoming harder to breathe" and 7 = "I am not getting enough air".

Statistical Analysis.

All dependent variables measured during submaximal exercise under the three experimental conditions were compared to the control gas (NOX) using a 4 (gas) x 6 (time) repeated measures ANOVA. Similarly, a 4 (gas) x 2 (time) repeated measures ANOVA was used for measures taken pre and post exercise. For both analyses, the alpha level was set *a priori* at 0.05. A Scheffe post-hoc multiple comparisons test was used if necessary, again with the alpha level set *a priori* at 0.05.

Results

All comparisons reported are between the experimental gas mixtures (HOX, HE-OX and HE-HOX) and NOX. This was consistent with the aim of the study which was to assess the effects of breathing the experimental gas mixtures compared to the standard practice of breathing compressed air with the SCBA. Selected results for ventilatory threshold and VO_{2max} from the graded exercise test are displayed in Table IV-2.

Measurements of Respiratory Work with the SCBA.

Peak expiratory mask pressure was significantly reduced during exercise with the helium mixtures (Fig. IV-1A). HOX also resulted in a lower expiratory mask pressure from 15 minutes onward compared to NOX. Consistent with the lower expiratory mask pressure during the HOX, HE-OX and HE-HOX trials, ventilatory mass moved was also significantly decreased with all three gases (Fig. IV-1B).

The significantly higher mean expiratory flow with HE-OX (Fig. IV-2A) and the reduced expiratory mask pressure with both helium mixtures led to a significant reduction in external breathing resistance during expiration with HE-OX and HE-HOX (Fig. IV-2B). With HOX, external breathing resistance during expiration was the same as NOX because the decrease in expiratory pressure was also accompanied by a lower mean expiratory flow ($p<0.05$, at 30 min).

Ventilatory Responses to Exercise

There was a progressive increase in V_E during all of the 30-minute trials. This was due to a progressive increase in breathing frequency while tidal volume remained consistent. Ventilation was similar for NOX, HE-OX and HE-HOX but was significantly lower with HOX at 20 and 30 minutes (Fig. IV-3A). The gas mixture did not affect breathing pattern as V_T, f, T_I and T_E were similar with all gas mixtures (Fig. IV-3B to IV-3E). Compared to the NOX trial (2240 ± 346 L), the total amount of gas mixture consumed was lower with HOX (2056 ± 318 L), higher with HE-OX (2417 ± 329 L) and unchanged with HE-HOX (2207 ± 308 L).

Heart Rate and Oxyhemoglobin Saturation Responses to Exercise

Heart rate and oxyhemoglobin saturation data are presented in Figure IV-4. Heart rate progressively increased during each of the 30- minute trials and tended to be lower with the hyperoxic mixtures but this was only significant at 5 minutes with HOX (Fig. IV-4A). The mean VO_2 throughout the NOX trial was 68 ± 5% of the compressed air VO_{2max}. The added stresses imposed by the protective clothing and the SCBA were far greater than "normal" exercise at this intensity. This is underscored by the heart rate responses which, at 30 minutes reached 98 ± 2% of the previously measured maximum heart rate. Oxyhemoglobin saturation significantly decreased from resting values with all four gas mixtures. Compared to breathing compressed air, oxyhemoglobin saturation was unchanged with HE-OX and was significantly higher with both hyperoxic mixtures (Fig. IV-4B).

Peak Mouth Pressures

Maximum inspiratory and expiratory pressures were significantly reduced after the NOX trial, and MEP was attenuated after the HOX trial (Table IV-3). In contrast, following the HE-OX and HE-HOX trials, neither MIP nor MEP significantly changed. As a result of the maintained MIP and MEP with the helium mixtures, post-exercise values were significantly higher than NOX.

Blood Lactate Measurements

Blood lactate concentrations (Bla^-) were similar at rest (Fig. IV-5) and rose significantly during exercise with all four gases. Blood lactate concentrations were similar for NOX and HE-OX, reaching 4.14 ± 1.98 $mmol \cdot L^{-1}$ and 4.18 ± 1.49 $mmol \cdot L^{-1}$ at 30 minutes, respectively. In contrast, Bla^- was significantly lower with the hyperoxic mixtures from the 15-minute sample onwards. The mean values for HOX and HE-HOX after 30 minutes were 3.01 ± 1.42 $mmol \cdot L^{-1}$ and 2.94 ± 1.34 $mmol \cdot L^{-1}$, respectively.

Psychophysical Responses to Exercise

At end exercise, RPE reached 16.7 ± 1.8 in the NOX trial, which corresponds to subjects perceiving the exercise to be "very hard" and underscores the severity of the exercise stress. During the HOX and HE-OX trials, RPE was not different to the NOX trial. However, at the end of the HE-HOX trial RPE was significantly lower ($p<0.05$), indicating that subjects perceived exercise to be easier with this gas mixture (Fig. IV-6A).

Despite the reductions in external expiratory breathing resistance, and expiratory mask pressure with the helium mixtures, and V_E and expiratory pressure with HOX, the experimental gas mixtures had no significant effect on the perceptions of respiratory distress (Fig. IV-6B).

Discussion

The main findings of this study demonstrated that, compared to NOX, breathing low density gas mixtures reduced expiratory mask pressure and decreased the external expiratory breathing resistance associated with the SCBA. Hyperoxia also reduced expiratory mask pressure, yet external expiratory breathing resistance was similar to breathing compressed air. The reduced external expiratory resistance observed with the helium-based mixtures can be explained by the physical properties of the gas. Gas flow through the regulator and the respiratory airways is either laminar or turbulent depending on airway radius, velocity of flow, and the viscosity and density of the gas mixture. As helium has a greatly reduced density and a viscosity only slightly higher than nitrogen, flow during helium breathing becomes turbulent or transitional at significantly higher flow rates than with air. This would decrease the resistance to gas flow through the SCBA regulator as observed in this study.

Respiratory Work with the SCBA

We are unaware of any previous investigation that has directly measured the respiratory work associated with the SCBA during exercise. Indeed, obtaining measures of the work of breathing with the SCBA would present some very difficult technical challenges. However, we report data to suggest that respiratory work is decreased when breathing helium-based gases from the SCBA compared to compressed air. The data displayed in Figures IV-1 to IV-3 show that at similar V_E and tidal volume, external expiratory breathing resistance, expiratory mask pressure and ventilatory mass moved with the helium mixtures were reduced, which provides strong evidence that the work of breathing against the SCBA regulator was decreased.

During heavy exercise conditions with the SCBA, it seems reasonable that the expiratory resistance increases the work of breathing and prolonged exposure may result in a reduced capacity of the respiratory muscles to generate force. The incidence of respiratory muscle fatigue has not been studied with the SCBA, but has been shown to occur when breathing against an external resistance (Aldrich, 1988) and even during exercise while mouth breathing (Johnson et al., 1986). It has also been demonstrated that reducing respiratory work with hyperoxia can decrease the occurrence of respiratory muscle fatigue (Bye et al., 1984).

To investigate whether the SCBA has the potential to reduce the respiratory muscles ability to generate pressure, a volitional maximal pressure test was performed before and after each trial. As this test relies on a volitional effort, the potential limitations of the technique to quantify fatigue should be acknowledged. However, maximal inspiratory pressure tests are considered to be reliable in highly motivated subjects (ATS, 2002) such as those that participated in this study. The significant reduction in maximal inspiratory and expiratory pressures following the exercise trials with NOX suggests that the SCBA may decrease the ability of the respiratory muscles to generate pressure. However, whether this is a long lasting fatigue that reduces ventilatory muscle performance or another mechanism such as a protective neural feedback loop to avoid fatigue within this important muscle group (Dempsey et al., 1988) cannot be determined. Post-exercise respiratory pressures were not changed after exercise with both helium mixtures, which provides evidence that respiratory muscle function was maintained throughout the 30 minutes of strenuous exercise.

Ventilatory Responses to Exercise

Despite the resistive unloading of the SCBA regulator with helium, there were no significant increases in V_E observed during the HE-OX and HE-HOX trials. This suggests that ventilatory limitation is unlikely with the SCBA at ventilation rates below 100 L·min^{-1}. However, V_E tended to be slightly elevated with HE-OX compared to NOX, resulting in a higher total volume of gas consumed ($p<0.05$) during the exercise period.

Therefore, HE-OX should decrease the total breathing time available on the SCBA tank, which may have some negative implications from an occupational safety perspective. Conversely, the significantly lower V_E with HOX reduced the total gas volume consumed and should prolong breathing time on the SCBA tank. Another interesting finding was that the volume of gas used in the HE-HOX trial was not significantly different from the compressed air trial, demonstrating that 40% O_2 appears to nullify the tendency to ventilate more with helium.

Psychophysical Stress and Blood Lactate

Even though a number of "stressors" such as expiratory mask pressure and ventilatory mass moved are reduced with HOX and HE-OX, the subjects only perceived the exercise to be easier at the end of the HE-HOX trial. A lower perceived exertion with HE-HOX suggests that the physical stress of exercise at the ventilatory threshold with the SCBA has been reduced, likely due to the combined effect of helium and hyperoxia on reducing respiratory effort and hyperoxia on reducing Bla^- concentration. However, further investigation is required to address whether the reductions in respiratory work and blood lactate can significantly improve work performance with the SCBA. It would seem likely that reductions in expiratory mask pressure and breathing resistance with the helium-based gases and the lower V_E and expiratory mask pressure with HOX, would result in a reduction in perceived respiratory distress but this was not the case. It is likely that a number of factors contribute to the overall perception of respiratory distress with the SCBA including inspiratory and expiratory resistance, ventilation rates, breathing frequency, obstruction of the natural oscillation of the thorax due to the shoulder straps and waist band of the harness, heat and the general fatigue experienced by the subjects. Therefore, even if some of the physiological components of respiratory stress are reduced, these differences may not alter the overall perception of breathing stress with the SCBA.

Summary

In summary, the results of the present study demonstrate that reduced density gas mixtures can decrease expiratory mask pressure and reduce the external expiratory breathing resistance imposed by the SCBA regulator. A reduction in the external expiratory breathing resistance has significant implications for reducing the work of breathing with the SCBA and may prevent the occurrence of respiratory muscle fatigue when repeated bouts of work are required.

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Table IV-1. Physical and Pulmonary Function Characteristics.

Age (yr)	Mass (kg)	Height (cm)	FEV_1 (%pred)	FEV_1/FVC (%pred)	MVV (%pred)
34 ± 10	77 ± 7	179 ± 5	108 ± 13	104 ± 6	103 ± 17

Values are means ± SD, n=15. *Abbreviations:* FEV_1 = Forced expired volume in 1 second, FEV_1/FVC = ratio of FEV_1 to forced vital capacity, MVV = maximum voluntary ventilation obtained during a standard pulmonary function test.

Table IV-2. Selected Variables Measured at Ventilatory Threshold and VO_{2max} with the SCBA and Compressed Air.

Condition	VO_2 ($L \cdot min^{-1}$)	V_E ($L \cdot min^{-1}$)	Heart Rate ($beats \cdot min^{-1}$)
Ventilatory Threshold	2.20 ± 0.30	63.6 ± 10.1	157 ± 12
Peak Exercise	3.45 ± 0.37	148.0 ± 17.3	189 ± 9

Values are means ± SD n=15. *Abbreviations:* VO_2 = oxygen consumption, V_E = ventilation.

Table IV-3: Maximal Inspiratory and Expiratory Mouth Pressures Generated Before and After the Exercise Trials.

Variable	NOX	HOX	HE-OX	HE-HOX
$MEP_{(Pre)}$, cmH_2O	214 ± 54	212 ± 49	206 ± 46	220 ± 50
$MEP_{(Post)}$, cmH_2O	187 ± 50†	189 ± 42†	205 ± 56*	207 ± 52*
$MIP_{(Pre)}$, cmH_2O	152 ± 42	160 ± 50	153 ± 41	158 ± 43
$MIP_{(Post)}$, cmH_2O	138 ± 45†	154 ± 48*	156 ± 40*	155 ± 46*

Mean ± SD for 15 subjects. Maximal expiratory (MEP) and inspiratory pressures (MIP). *= Significant difference from NOX ($p<0.05$). † = Significant difference from pre-test values ($p<0.05$).

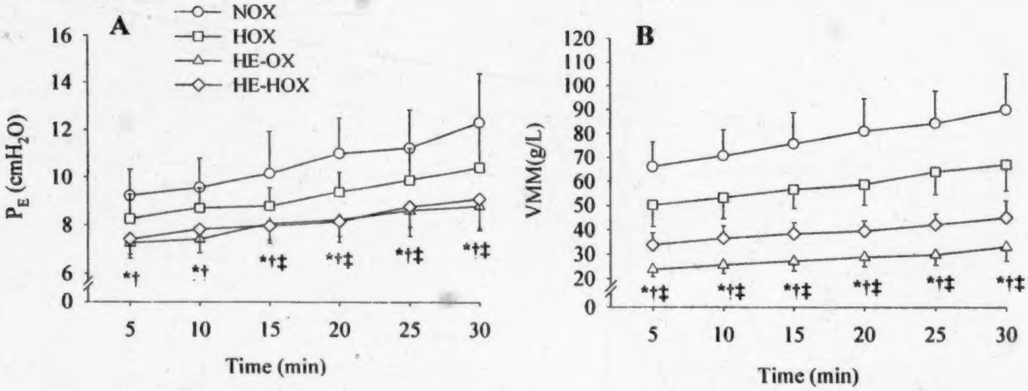

Figure IV-1: Selected markers of respiratory effort, namely expiratory pressure (P_E) and ventilatory mass moved (VMM), measured throughout the exercise trials with the different experimental gas mixtures. n = 15. * = HE-OX vs. NOX ($p<0.05$); † = HE-HOX vs. NOX ($p<0.05$); ‡ = HOX vs. NOX ($p<0.05$).

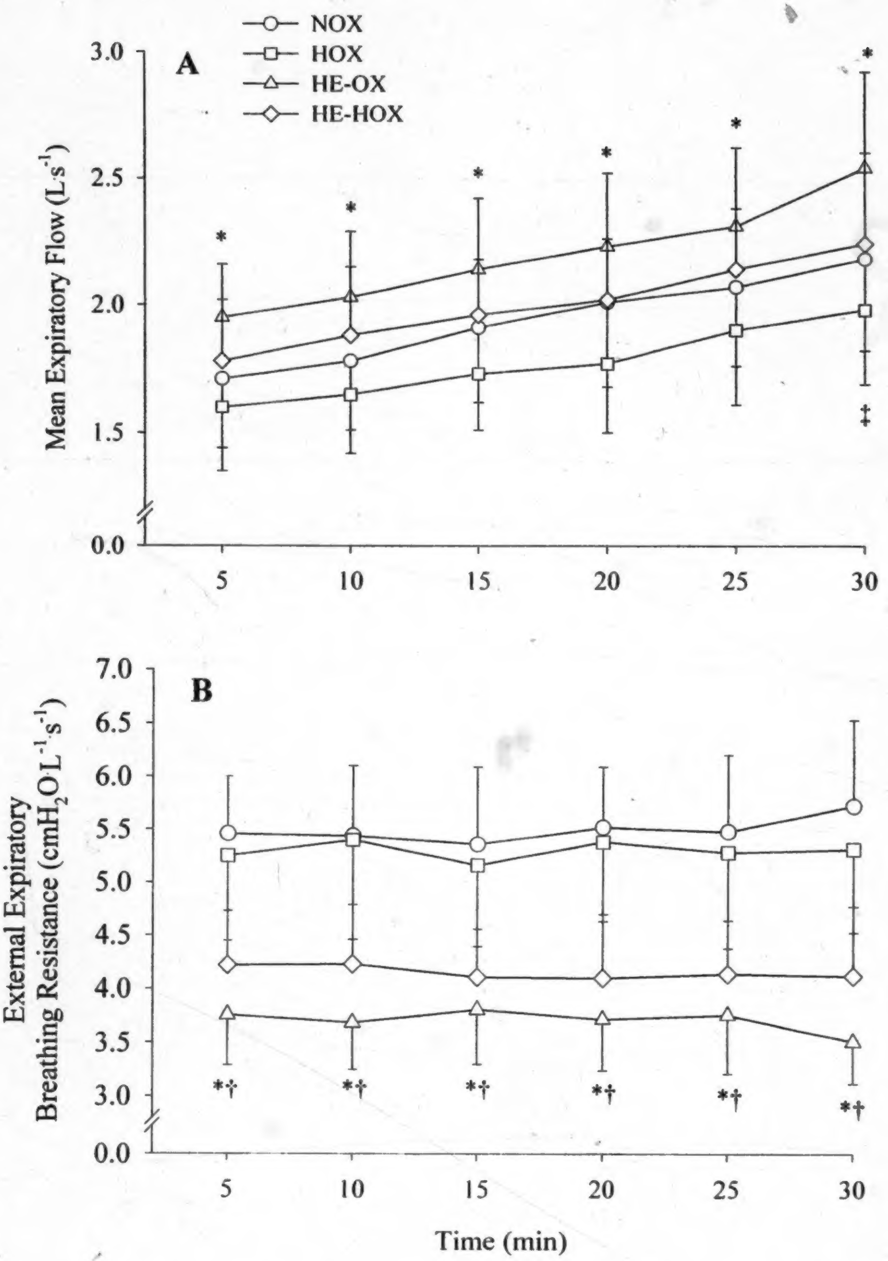

Figure IV-2: The effect of the experimental gas mixtures on mean expiratory flow and external expiratory breathing resistance measured during the exercise trials. n = 15. * = HE-OX vs. NOX ($p<0.05$); † = HE-HOX vs. NOX ($p<0.05$); ‡ = HOX vs. NOX ($p<0.05$).

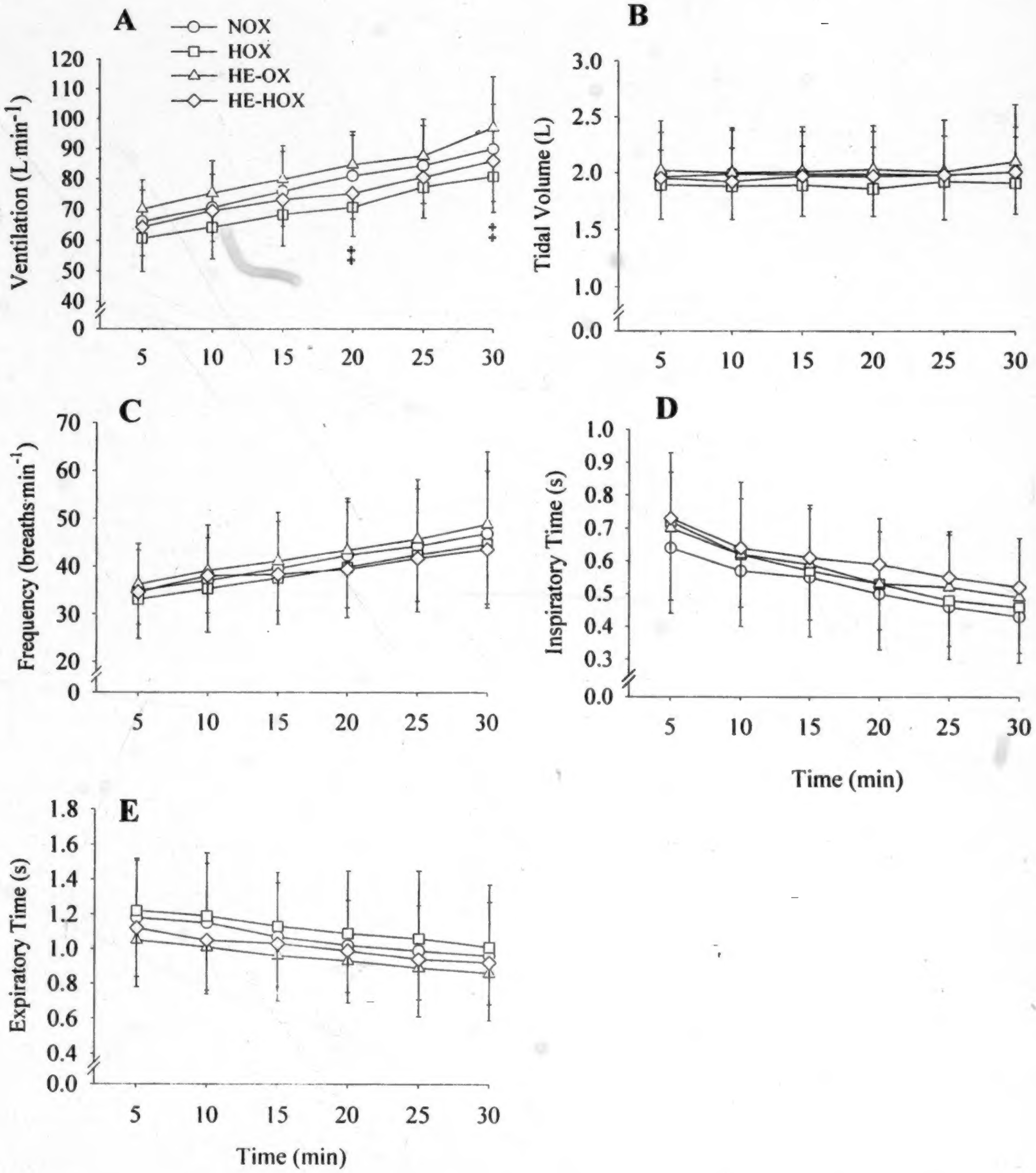

Figure IV-3: Ventilatory responses to the different experimental gas mixtures during the exercise trials with the SCBA. n = 15. ‡ = HOX vs. NOX ($p<0.05$).

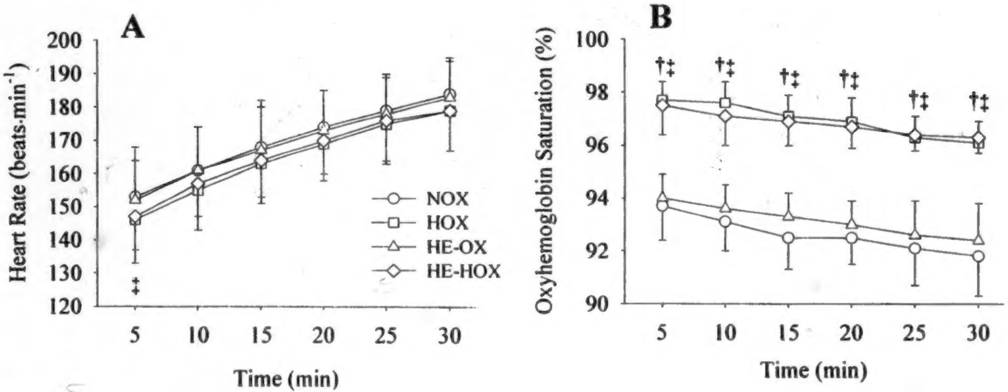

Figure IV-4: Heart rate and oxyhemoglobin responses measured during the exercise trials breathing the differ mixtures $n=15$. † = HE-HOX vs. NOX ($p<0.05$); ‡ = HOX vs. NOX ($p<0.05$).

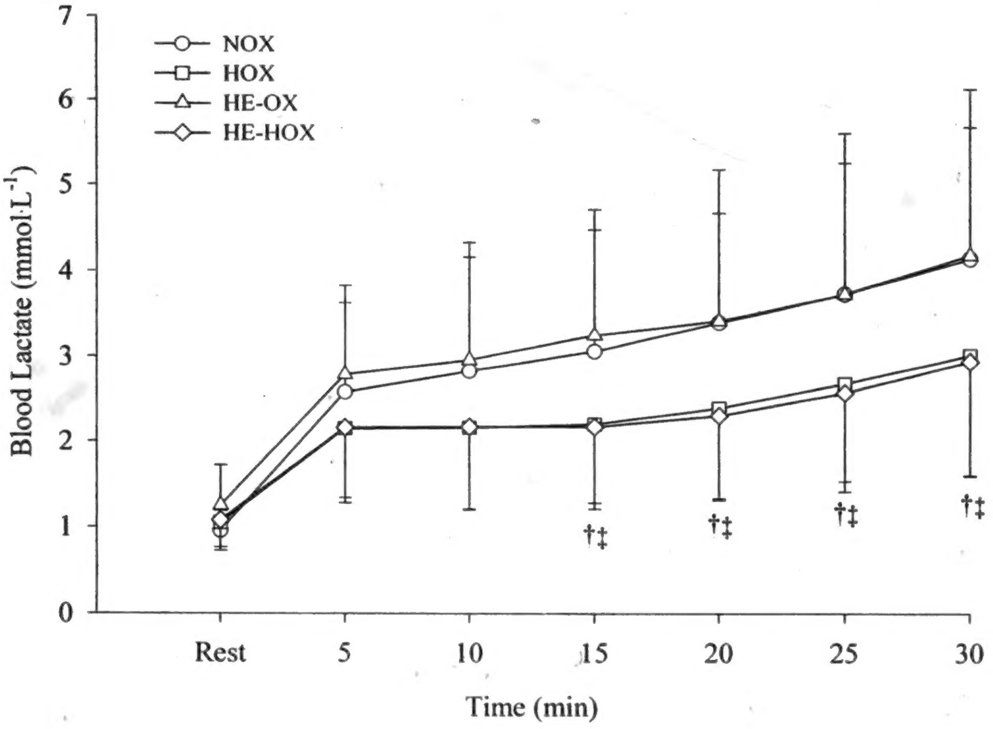

Figure IV-5: Blood lactate responses measured during the exercise trials with the different gas mixtures. n=13. † = HE-HOX vs. NOX ($p<0.05$); ‡ = HOX vs. NOX ($p<0.05$).

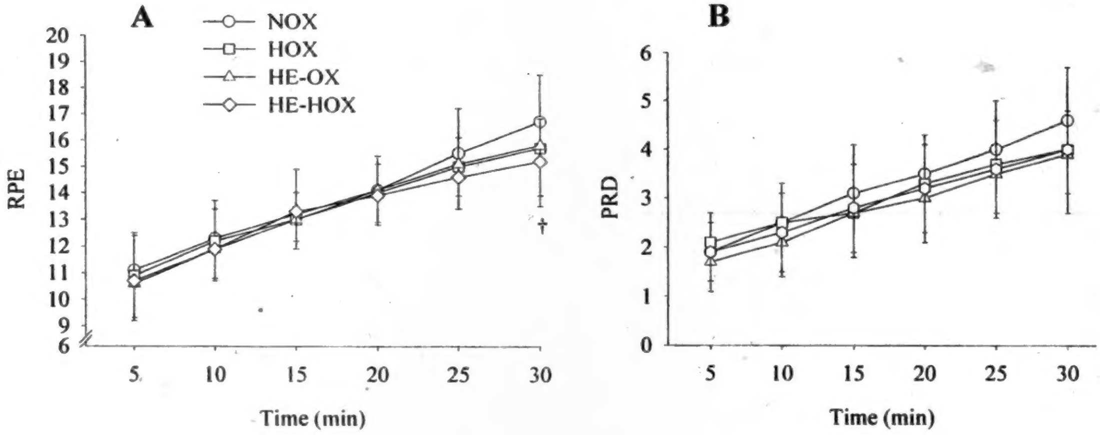

Figure IV-6: Rating of perceived exertion (RPE) and perceived respiratory distress (PRD) measured during the exercise trials with the different gas mixtures. n = 15. † = HE-HOX vs. NOX ($p<0.05$)

CHAPTER V

The Effects of Helium and Hyperoxia on Exercise Tolerance and Cardiopulmonary Function in Chronic Obstructive Pulmonary Disease.

Introduction

Individuals with chronic obstructive pulmonary disease (COPD) have a reduced exercise tolerance (Jones et al., 1971; O'Donnell et al., 1993, 2001a; Mitlehner and Kerb, 1994; Oelberg et al., 1998), with exercise often being terminated prematurely due to exertional dyspnea. The mechanisms responsible for the adverse symptom of dyspnea are likely multifactorial in nature. However, a growing body of evidence (O'Donnell et al., 1993, 1997, 2001a; Murciano et al., 2000; Diaz et al., 2000; Marin 2001) has identified a strong relationship between the degree of dynamic hyperinflation and the intensity of dyspnea experienced by these patients. As end expiratory lung volume rises (EELV) during exercise, end inspiratory lung volume (EILV) also increases in an attempt to augment tidal volume. This elevation in EILV reduces inspiratory reserve volume (IRV) and moves tidal breathing onto the flatter, less compliant portion of the pressure-volume curve (Yan et al., 1997a). As a consequence, the elastic work of breathing is increased, while the respiratory muscles are placed at a mechanical disadvantage to generate pressure (Yan et al., 1997b, Sharp, 1983). Secondly, any increase in EELV above relaxation volume results in an intrinsic positive alveolar pressure at end expiration (PEEPi), which must be overcome before inspiratory flow can start (Sliwinski et al., 1998). Thus the increase in lung volume increases the elastic work of breathing while concomitantly reducing the respiratory muscles ability to generate pressure. The resulting mismatch between respiratory effort and ventilatory output has been implicated as a primary mechanism for dyspnea in this population (Leblanc et al., 1986; O'Donnell et al., 1993).

Cardiovascular function has often been overlooked as a limiting factor to exercise in COPD patients because exercise is frequently terminated by symptom limitation and poor motivation before the maximal capacity of the cardiovascular system has been reached. However, even in the absence of coronary artery disease, a number of studies have demonstrated abnormal cardiovascular responses to exercise (Mahler et al., 1984; Morrison et al., 1987; Slutsky, 1981; Montes de Oca et al., 1996; Oelberg et al., 1998). It is possible that increased operational lung volumes and deranged pulmonary mechanics associated with COPD maybe adversely affect cardiac function (Potter et al., 1971; Butler et al. 1988; Ranieri et al., 1996). As the lungs and heart occupy a limited volume within the thorax, progressive dynamic hyperinflation with exercise may limit intrathoracic space and hinder cardiac filling through a reduction in ventricular compliance. Additionally, the large negative swings in pleural pressure as a result of breathing at elevated lung volumes and overcoming PEEPi may enhance right ventricular (RV) preload while increasing RV and left ventricular (LV) afterload (Ranieri et al., 1996). In the presence of dynamic hyperinflation, an increase in RV end diastolic volume, without an increase in RV ejection fraction (Mahler et al., 1984; Morrison et al., 1987) could result in ventricular interaction and reductions in LV compliance and filling. Although there is no conclusive evidence for this hypothesis, there is definitely grounds to further investigate the role of cardiac function in the exercise limitation of COPD patients.

Previous work by O'Donnell (1997a, 2001b) and others (Somfay et al., 2001) has demonstrated that breathing hyperoxia reduces ventilatory demand, increases expiratory time and delays dynamic hyperinflation, which leads to a reduction in dyspnea and improved exercise tolerance in COPD. However, at symptom-limitation with hyperoxia, operational lung volumes, ventilation and dyspnea are unchanged from breathing air, indicating that the ventilatory constraints to exercise are delayed with hyperoxia but not improved (O'Donnell et al., 2001b). In contrast, the use of a normoxic helium gas has been shown to increase peak expiratory flow rates and improve maximal ventilation (Oelberg et al., 1998; Richardson et al., 1999). However, the effects of a normoxic-helium mixture on dynamic hyperinflation, the work of breathing and submaximal exercise tolerance are currently not known. Furthermore, breathing a helium-hyperoxic gas mixture could combine the benefits of both helium and hyperoxia and have a greater effect on exercise tolerance. To our knowledge the potentially greater benefits of helium hyperoxia on exercise tolerance, the work of breathing and cardiovascular function have also not been studied.

In this study, we tested the hypothesis that helium-hyperoxia (HE-HOX) would increase exercise tolerance to a greater extent than hyperoxia (HOX) or normoxic helium (HE-OX) in COPD patients. In addition, in order to identify the mechanism(s) responsible for any increase in exercise tolerance found with the helium-hyperoxic gas we tested two subsidiary hypothesis: 1) that HE-HOX would have a greater effect on dynamic hyperinflation, work of breathing and dyspnea than HOX or HE-OX and 2) That HE-HOX would have a greater effect on LV end diastolic cavity area and LV systolic function than both the other gas mixtures.

Methods

Participants

Eleven clinically stable males with moderate to severe COPD (FEV_1 = 46 % predicted, FEV_1/FVC= 55 ± 10% predicted) volunteered for the study. All participants had completed the pulmonary rehabilitation program at the Centre for Lung Health at the Edmonton General Hospital and were familiar with symptom-limited incremental exercise, and exertional symptom evaluation. Individuals dependent on supplemental oxygen, with cardiovascular disease and/or musculoskeletal abnormalities known to affect exercise were excluded from the study. Ten of the eleven had a smoking history (61 ± 38 average pack years: 10.4 ± 8.6 yr since quitting for 9 subjects). Before commencing the study, participants were fully informed of all aspects of the research project and signed an informed consent in accordance with the requirements of the Health Research Ethics Board at the University of Alberta Hospital. Subject characteristics and pulmonary function data are presented in Table V-1. Power calculations to determine sample size were performed before the study to estimate an adequate sample size for expected changes in the primary outcome.

Study Design

The study was a randomized, single blind, crossover design, which required four separate visits to the University of Alberta. In the initial visit participants performed a pulmonary function test with blood gas analysis and a symptom-limited incremental exercise test. The second visit consisted of four exercise bouts to evaluate the effect of the experimental gas mixtures on cardiovascular function. In the final two visits, participants performed two constant load exercise tests to exhaustion (four in total) to examine the effect of the three experimental gas mixtures on exercise tolerance and exercise pulmonary function. During the study, participants were asked to refrain from exercise in the 24 hours before a test and to avoid alcohol and caffeine on testing days. The one smoker was also asked to refrain from smoking on testing days.

Inspired Gas Mixtures

The four gas mixtures studied were: air (21% O_2, 79% N_2); hyperoxia (HOX: 40% O_2, 60% N_2); normoxic-helium (HE-OX: 21% O_2, 79% He) and helium hyperoxia (HE-HOX: 40% O_2, 60% He). Participants were blinded to the gas mixture used and were requested to not talk during, or for a short period after, exercise due to the change in the vocal tone with helium. Gases were delivered from large cylinders that were always covered or hidden from the view. All gases were passed through a humidifier (Model H2-500, Fisher & Paykel, Laguna Hills, CA) into a large reservoir bag, before being delivered to the patient through a standard low resistance two-way breathing valve (Hans-Rudolph 2700, Kansas City, MO).

Experimental Protocols

Pulmonary Function Testing: To ascertain the severity of COPD, routine pulmonary function variables and single-breath diffusion capacity for carbon monoxide (D_{LCO}) were measured in the sitting position according to American Thoracic Society guidelines. Baseline lung volumes were determined using a constant-volume body plethysmograph (6200 Autobox; SensorMedics, Yorba Linda CA). Total lung capacity was then calculated as the sum of functional residual capacity and inspiratory capacity. Spirometry values were compared to the reported norms of Crapo et al., (1981), DLCO was compared to the norms of Miller et al., (1983), and lung volume values was compared to Goldman and Becklake (1959). Additionally, resting arterial blood gases (P_aO_2 and P_aCO_2), and pH were measured from the radial artery at rest while breathing room air.

Incremental Exercise Test: To determine VO_{2peak} and to confirm that participants were free from any cardiovascular contraindications to exercise, a physician-supervised stress test was performed prior to inclusion in the study. Participants were seated on an electrically braked cycle ergometer and expired gases were analyzed by a calibrated metabolic measurement system (Medigraphics, Parvo, Salt Lake City, UT). After stable resting metabolic values were achieved, subjects cycled at 10W and the load was increased by 5-10 $W \cdot min^{-1}$ until symptom-limitation. This protocol has been demonstrated to be appropriate for measuring VO_{2peak} in this population (O'Donnell et al., 2001a). During exercise, pulse oximetry and heart rate were monitored continuously, while blood pressure, dyspnea and leg discomfort were measured every two minutes. At end exercise, participants were asked to specify why they stopped exercising.

Evaluation of Cardiovascular Function During Exercise: To evaluate the effect of each gas mixture on LV function, four bouts of exercise were performed on an upright, cycle ergometer. Before each trial, participants breathed the test gas mixture until resting metabolic parameters became stable. Once steady state had been achieved a qualified cardiac sonographer used two-dimensional echocardiography to measure left ventricular systolic function (Sonos 2500; Hewlett Packard; Avondale, PA). Exercise was then performed at 62 ± 4%, (70 ± 25W) of peak power output. After four minutes of exercise, blood pressure was recorded and the echocardiographic assessments were repeated. Following the echo assessment dyspnea and leg discomfort were recorded before the test was stopped. Participants then sat in a comfortable chair breathing room air for approximately ten minutes while the investigators changed the experimental gas mixtures and recalibrated the metabolic measurement system. Once heart rate and blood pressure had returned to previous resting values, the protocol was repeated three more times with each of the remaining gases. The four gas mixtures were administered in random order and all gas tanks were hidden by a curtain pulled across the laboratory (Figure A4 and A5, Appendix A).

Exercise Tolerance and Exercise Pulmonary Function: Before performing the exercise tolerance tests a balloon tipped catheter was inserted for the measurement of esophageal pressure and the spirometry tests were repeated to ensure that no changes in resting pulmonary function occurred between the two test days. The test gas mixture was then breathed until resting metabolic parameters became stable. Once steady state was achieved flow-volume loops, resting ventilatory parameters and inspiratory capacity were measured. Participants then exercised at the same intensity as in the exercise echocardiographic assessments until symptom limitation. A cadence between 50 and 70 rpm was self selected and maintained throughout each trial. Operational lung volumes, blood pressure and exertional symptoms were measured every two minutes, heart rate and oxyhemoglobin saturation were recorded continuously. To allow measurement of metabolic data and inspiratory capacity subjects were switched between the metabolic measurement system and a "bag in box" system (Figure A6-A8, Appendix A). The box was connected to a low resistance spirometer so that the inspired and expired volumes could be measured.

Following exercise termination, subjects rested for 60-90 minutes, before the test was repeated with a different gas mixture. Subjects then returned at a similar time of day to repeat the remaining two tests. Test days were separated by at least 48 hours and were generally repeated within one week of the initial constant load trial. During each test, two research assistants blinded to the gas mixture used, gave a similar level of encouragement. Furthermore, participants were not told their exercise time or any other results until their participation in the study was completed.

Specific Testing Procedures

Measurement of Gas Exchange and Ventilation: During all exercise tests expired gases were analyzed for metabolic [VO_2, VCO_2 and respiratory exchange ratio (RER)] and ventilatory parameters [V_E, tidal volume (V_T), breathing frequency (f), inspiratory (T_I) and expiratory (T_E) time]. The gas analyzers were calibrated before each test and verified immediately after using primary standard gases containing appropriate concentrations of O_2 and CO_2 and either N_2 or He. The pneumotachometer (Hans Rudolph, Kansas City, MO) of the metabolic measurement system was also calibrated with each of the experimental gases at varying flow rates. Prior to each test, a volume validation was performed using the test gas mixture to ensure measured volumes were within an acceptable range (<1% error).

Measurement of Esophageal Pressure and the Work of Breathing: Esophageal pressure was measured with a 10-cm latex balloon catheter (Ackrad Laboratories Inc., Cranford, NJ) positioned in the lower third of the esophagus (For a more detailed description of this technique see Appendix B). Esophageal pressure and mouth pressure were then measured using Validyne transducers (Validyne MP45) that had been calibrated before each test. Signals were amplified, changed to a digital signal (Powerlab ML785, ADI Instruments, Colarado Springs, CO) and sampled on a computer at 100Hz.

A detailed description of the technique used for evaluating the individual components of the work of breathing are presented in Appendix B. Assuming a normal chest wall compliance for patients with COPD (Sharp et al., 1968, Fleury et al., 1985) the static pressure-volume curve of the chest wall was obtained from the literature (Estenne et al., 1983) taking the age and sex of our subjects into consideration. This relationship was then positioned using a similar technique to Yan et al., (1997) and Sliwinski et al., (1998). The esophageal pressure-volume loops during tidal breathing were transposed onto the static chest wall pressure-volume compliance curve and the points of zero flow at the start and end of inspiration were joined to identify dynamic lung compliance.

The resistive work of breathing performed on inspiration was calculated as the area enclosed by the dynamic esophageal pressure-volume loop and the dynamic lung compliance line (Figure B-2, Appendix B). The inspiratory elastic work to overcome PEEPi (W_{IP}) and the portion of elastic work required to overcome the elastic recoil of the lung or the non-PEEPi elastic load (W_{INP}) were then calculated. (Sliwinski et al., 1998). Additional work performed by the respiratory muscles during expiration was also calculated as the area enclosed by the dynamic esophageal pressure-volume loop that lay to the right of the static chest wall compliance line (Figure B-1). This process was performed on three esophageal-pressure volume loops at rest, symptom limitation and at all three isotimes for each individual. The plots were then imported into a commercially available software package (Image-Pro Plus, Media Cybernetics, Silver Spring, MD) and the areas were calculated. These results were averaged and reported both as the work performed per breath and as a minute average by taking breathing frequency into consideration.

Measurement of Operational Lung Volumes: Previous studies have demonstrated that TLC does not change with exercise (Stubbing et al., 1980; Yan et al., 1997c) and that inspiratory capacity maneuvers are a simple and reliable method for estimating changes in EELV in COPD patients (Dolmage et al., 2002; Yan et al., 1997c). Therefore, to estimate EELV (TLC - IC) and inspiratory reserve volume (IC – V_T), subjects performed a minimum of three IC maneuvers at rest and every two minutes during each of the exercise tolerance trials. For these measurements tidal volume was averaged over the last six breaths before the inspiratory capacity maneuver was performed. To ensure subjects could reproduce satisfactory IC maneuvers a practice session was included before the first exercise tolerance trial. Additionally, to guarantee that the IC maneuvers were performed to TLC during exercise, the esophageal pressure achieved at the peak inspired volume plateau (zero flow) was compared during exercise to resting values (Yan, et al., 1997c).

Exercise Echocardiography Measurements: All echocardiographic measures were performed using a Hewlett-Packard ultrasound instrument (Sonos 2500, Hewlett-Packard, Avondale, PA) with a 3.5-MHz transducer. Two-dimensional images of the left ventricle were collected in the parasternal short axis view at the level of the papillary muscle and averaged over three cardiac cycles to measure: end systolic cavity area (ESCA); end-diastolic cavity area (EDCA); end systolic total cavity area (ESTA, the total area enclosed by the epicardium); end systolic myocardial area (ESMA = ESTA-ESCA); stroke area (SA = EDCA-ESCA) and fractional area change (FAC = SA/EDCA). Knowing cavity area, LV dimensions were calculated and then used to calculate end diastolic and end systolic volumes using the Teichholz formula (Teichholz, et al., 1976). From these volumes, stroke volume (LVEDV-LVESV) and ejection fraction were calculated (SV/LVEDV). Heart rate was continuously measured and averaged over a minute and cardiac output was calculated from the product of heart rate and stroke volume. Left ventricular end systolic transmural pressure was estimated from end systolic pressure minus esophageal pressure (Haykowsky et al., 2001). For this calculation end-expiratory pressure was used, as this is where the clearest echocardiographic images could be obtained. Left ventricular end systolic wall stress was then calculated as 1.33 x end systolic transmural pressure x [ESCA/ESMA]) and LV contractility was estimated using left ventricular end systolic transmural pressure/ESCA.

Evaluation of Exertional Symptoms: At the end of each workload in the graded exercise tests, after the exercise echocardiographic assessment had been performed and every two minutes in the exercise tolerance trials, exertional dyspnea and leg discomfort were evaluated using the Borg scale. On termination of the graded exercise test and the exercise tolerance trials, participants were ask what symptom was responsible for stopping exercise.

Data Analysis

The main aim of this study was to determine if helium-hyperoxia has a greater effect on the exercise tolerance, operational lung volumes, work of breathing and cardiovascular function of COPD patients than either normoxic-helium or hyperoxia. In order to answer these questions, a one way repeated measures ANOVA was performed for all dependent variables measured at symptom limitation, and at three specific isotimes within the exercise tolerance trials. The three isotimes studied were as follows: isotime 1 (IT1) – A time comparable to when the echocardiographic measurements were made, isotime 2 (IT2) – A time comparable to exercise termination in the air trial and isotime 3 (IT3) – A time comparable to end exercise in the hyperoxic trial terminated first. When the ANOVA detected a significant effect, a Tukey post hoc multiple comparisons test was performed.

To ascertain any association between changes in exercise tolerance and improvements in cardiopulmonary function and/or dyspnea, simple regression analysis using Pearson correlations was performed. The change in time to symptom-limited endurance with the each gas mixture was set as the dependent variable and changes in operational lung volumes, ventilation, work of breathing, cardiovascular parameters and exertional symptoms were used as independent variables. In addition, the strongest significant contributors to the improvement in exercise tolerance were selected by multiple stepwise regression analysis. The same analysis was also performed to ascertain the best predictors of dyspnea, the changes in dyspnea with each gas and factors responsible for changes in exercise cardiovascular function. For all analysis and post hoc comparisons the alpha level was set *a priori* at 0.05.

Results

Ten of the eleven subjects terminated all four-exercise trials due to symptom limitation. One subject was prematurely stopped in his final exercise trial due to atrial fibrillation caused by a previously undiagnosed hyperthyroid condition. Therefore, end exercise comparisons are made between ten subjects. However, all eleven data points are included at rest and the first isotime, as these data points were completed with all four gas mixtures before the irregular cardiovascular episode occurred.

Symptom-Limited Exercise Tolerance

The effect of each gas mixture on exercise tolerance is depicted in Figure V-1. A significant increase in exercise capacity was found with all three gas mixtures compared to breathing air. Symptom limitation terminated exercise after 9.4 ± 5.2 min on air, 17.8 ± 5.8 min on HOX and 16.7 ± 9.1 min on HE-OX. The combination of helium and hyperoxia had a significantly greater effect on exercise tolerance than all other gases, as subjects performed 26.3 ± 10.6 min with the HE-HOX gas. The individual exercise responses on each gas mixture are presented in Figure V-2. Compared to air, all ten subjects improved their exercise times on HE-OX and HE-HOX, while nine subjects improved on hyperoxia. Additionally, eight out of ten subjects improved their exercise tolerance when breathing HE-HOX compared to breathing HOX ($p<0.05$).

At the end of the air trial, dyspnea was the primary reason for stopping exercise in eight subjects, while two stopped due to leg discomfort. In contrast, leg discomfort was reported as the principal reason for exercise termination with HOX (n=5), HE-OX (n=4) and HE-HOX (n=7), with four, three and two subjects stopping primarily due to dyspnea, respectively. Additionally, two subjects reported the combination of leg discomfort and dyspnea as the primary reason for stopping in the HE-OX trial. One subject stopped due to "other" reasons with each of the experimental gas mixtures. These reasons included loosing control of the mouthpiece (HOX), general fatigue (HE-OX) and discomfort from the bicycle seat (HE-HOX). At end exercise, exertional dyspnea was not significantly different between the air trial and the two hyperoxic gases (Table V-5, Figure V-3A). However, with HE-OX, exertional dyspnea was significantly lower at end exercise (Borg ratings of 4.9 vs. 5.8 on HE-OX and air, respectively). No significant difference in leg fatigue was observed at test termination and ranged from 5.2 with air to 5.6 with HE-HOX. (Table V-5, Figure V-3B)

Throughout the exercise tolerance tests, exertional dyspnea was significantly decreased with all three experimental gases at the first and second isotimes. HE-HOX also reduced dyspnea at the first and third isotime compared to HE-OX and HOX, respectively ($p<0.05$). In addition to the reductions in dyspnea, the two hyperoxic gas mixtures also reduced leg discomfort at the first two isotimes compared to air. The reductions in leg discomfort with HE-HOX were also significantly lower than HE-OX at isotime 2 (Figure V-3A).

Metabolic Responses to Exercise

The metabolic responses to exercise are presented in Figure V-4. At symptom-limitation, VO_2 was 17.2 $ml \cdot min^{-1} \cdot kg^{-1}$ in the air trial, which was equivalent to 96% of the VO_{2peak} achieved during the incremental exercise test breathing air (Table V-2). With the other three gases, VO_2 was not significantly different from air at the end of each trial and reached 18.0, 18.1 and 18.5 $ml \cdot min^{-1} \cdot kg^{-1}$ on HOX, HE-OX and HE-HOX, respectively. At rest and at the first two isotimes, VO_2 was similar between the four gas mixtures. However, at the third isotime, VO_2 was significantly reduced with HE-HOX compared to the HOX trial. In combination with the similar VO_2 observed with each gas, VCO_2 and RER were also not significantly different at rest or during exercise with any gas.

Oxyhemoglobin measurements taken at rest and during each exercise trial are presented in Figure V-4. Administration of both hyperoxic mixtures increased S_pO_2 at rest and throughout exercise compared to air and HE-OX. With the normoxic gas mixtures, S_pO_2 decreased significantly from resting values to end exercise. However, S_pO_2 was maintained throughout the HOX and HE-HOX trials, as S_pO_2 at end exercise did not differ from resting values ($p>0.05$).

Ventilatory Responses to Exercise

The ventilatory responses to exercise are presented in Table C-1 (Appendix C) and Figure V-5. There was no significant difference in any ventilatory parameter at rest. V_E, tidal volume and breathing frequency were all increased over resting values with exercise. However, there was only a significant increase in tidal volume between rest and the first isotime with all four-gas mixtures. V_E did not increase after isotime one with air. However, with the three experimental gases V_E significantly rose from isotime one to test termination.

During exercise, the hyperoxic gas mixtures reduced V_E predominantly through a decrease in respiratory rate ($p<0.05$). Despite the lower V_E, tidal volume was significantly enhanced with HE-HOX at the second isotime, predominantly due to a decrease in EELV. The reduction in breathing frequency throughout exercise with the hyperoxic mixtures resulted in a significantly longer expiratory time with HOX at isotime one, while HE-HOX increased inspiratory and expiratory time at the first and second isotimes, respectively. Duty cycle or T_I/T_{TOT} (inspiratory time/total time) only significantly decreased from rest to exercise with the helium mixtures. However, T_I/T_{TOT} was similar to air with HOX and HE-HOX. In contrast at end exercise with HE-OX, duty cycle was significantly reduced even though inspiratory and expiratory times were not significantly different from the other gases.

At symptom limitation, there was no difference in any ventilatory parameter between air and HOX. In contrast, V_E was significantly increased with HE-OX by 16 ± 16% compared to both air and HOX due to an enhanced tidal volume (1.90 L vs. 1.69 L, in HE-OX and air, respectively). There was considerable variation in the individual ventilatory responses observed with helium as V_E at end exercise with HE-OX ranged from 97 to 146% of V_E with air. The change in V_E with HE-OX significantly correlated with FEV_1 ($r = 0.80$) and FEV_1 as a percentage of predicted ($r = 0.64$). At end exercise with HE-HOX, V_E was not different from any other gas. However, as with HE-OX, tidal volume was enhanced by 0.15L ($p<0.05$).

Operational Lung Volume Responses to Exercise

At rest, IC, EILV and IRV were unchanged from the air trial with all three gas mixtures (Table V-3, Figure V-6 and V-7). From quiet breathing at rest to symptom limitation, all patients dynamically hyperinflated as demonstrated by the significant reduction in IC and thus an increase in EELV. The rise in EELV during exercise resulted in a mean PEEPi at end exercise of 4.2 ± 2.1 cm H_2O in the air trial (range 0.7 – 7.7 cm H_2O). At symptom limitation, there was no difference in IC, EILV, IRV or PEEPi with any gas. However, it should be reiterated that there was an improvement in tidal volume with both the helium gas mixtures predominantly due to a reduced EELV. At end exercise, EILV reached 94% of TLC in all trials, which highlights the marked reduction in IRV.

At the first isotime, IC was significantly increased with HOX, HE-OX and HE-HOX. In addition, the degree of DH with HE-HOX was significantly improved compared to HOX, as demonstrated by a greater IC in the hyperoxic-helium condition (2.55 L vs. 2.40 L, $p<0.05$). Concomitant to the reduction in DH with the helium gases, PEEPi was reduced from 3.7 cm H_2O in air to 2.2 and 2.0 cm H_2O with HE-OX and HE-HOX, respectively. This reduction in PEEPi with HE-HOX was also different from HOX (3.2 cm H_2O, $p<0.05$). The reduction in DH, with HE-HOX was also associated with a significantly reduced EILV, and an enhanced IRV, compared to air. Even though DH was lower with HE-OX, EILV and IRV were not different from air breathing due to the increase in tidal volume.

Inspiratory capacity was increased and PEEPi decreased with both helium mixtures at the second isotime (Figure V-7). IC was not different with HOX (p=0.06) even though the extent of DH was significantly reduced from breathing air. Comparable, to HE-OX at the first isotime, the reduction in EELV with both helium gases did not result in a decrease in EILV as tidal volume was enhanced at the expense of the IRV.

Expiratory Flow Limitation with the Experimental Gas Mixtures

Throughout exercise, tidal expiratory flows met or surpassed the maximal flow volume loop when breathing air in all subjects. During exercise with the three experimental gases, expiratory flow limitation was reduced. However, the mechanism response for this reduction was different depending on whether the gas was helium-based or contained hyperoxia. With HOX, peak and mean expiratory flow rates were decreased compared to air (Table V-5, Figure V-8). In contrast, the maximal flow-volume envelope was enhanced with HE-OX and HE-HOX (Figure V-8), mainly through an increase in maximal expiratory flow rates. At isotime 1 and 2 with HE-OX, peak and mean tidal expiratory flow rates were not enhanced during tidal breathing, however, the combination of a 14% increase in expiratory time with a 6% increase in MEF maintained EELV closer to resting EELV. At end exercise, both peak inspiratory and expiratory flow rates were increased as tidal breathing utilized the enhanced maximal flow-volume envelope to increase V_E.

Similar to HOX, expiratory flow limitation was reduced with HE-HOX. This was mainly due to a reduction in peak expiratory flow rate during tidal breathing, as mean flow rates did not differ from air at any time during exercise (Table C-2, Appendix C). Like HE-OX, the maximal flow volume loop was enhanced with HE-HOX. However, it would appear that the potential for improving expiratory flow was not utilized as neither peak nor mean expiratory flow rates differed from breathing air at symptom limitation in this study.

Work of Breathing Responses to Exercise

The work of breathing during exercise was measured in nine subjects and is presented in Table V-4 and Figures V-10. At rest, both helium mixtures reduced the resistive work of breathing compared to air ($p<0.05$). Additionally, the total elastic work of inspiration was significantly reduced with HOX and HE-HOX. This reduction in total inspiratory elastic work was predominantly due to a reduction in W_{INP}, as the work to overcome PEEPi was not different between conditions. When the total work of breathing per minute was calculated only HE-HOX was significantly different from air.

At the first isotime during exercise, resistive work was significantly decreased by 28 ± 18%, 33 ± 16% and 36 ± 17 % with HOX, HE-OX and HE-HOX, respectively (Figure V-10A). In combination with the reduction in EELV observed with all three experimental gas mixtures, W_{IP} was also reduced from 7.2 L.cm H_2O^{-1} with air to 5.5, 3.5 and 3.1 L.cm H_2O^{-1} with HOX, HE-OX and HE-HOX, respectively. This reduction in W_{IP} with the two helium gases was also different from HOX ($p=0.05$) (Figure V-10B). The inspiratory work done to overcome the elastic properties of the respiratory system

(W_{INP}) was not significantly reduced with HE-OX and HE-HOX but was lower with HOX (Figure V-10C). Collectively, the combined reductions in W_{IP} and W_{INP} with HE-HOX meant that the total elastic work of breathing was reduced (33.1 vs. 24.8 L·cm H_2O^{-1} in air and HE-HOX, respectively) (Figure V-10D). The total elastic work of breathing was also reduced with HOX but this was not the case with HE-OX. Furthermore, the total work of breathing per minute was decreased by 33 ± 23%, 32 ± 11% and 38 ± 17% with HOX, HE-OX and HE-HOX, respectively ($p<0.05$) (Figure V-10E)

At isotime 2, the resistive work of breathing and the work of breathing to overcome PEEPi were only reduced with HE-HOX ($p<0.05$). There were also no significant differences in W_{INP} with any gas mixture. When the total resistive and elastic components of the work of breathing were averaged over a minute, both parameters were reduced with HOX and HE-HOX, due in part to the significant reductions in breathing frequency. However, the total work of breathing was only significantly reduced with HE-HOX due to a slight, but non-significant increase in the additional expiratory work of breathing performed with HOX (Table V-4). At isotime three and at symptom limitation, no differences were observed in the work of breathing for any gas mixture.

Cardiovascular Responses to Exercise

Satisfactory two-dimensional echocardiographic assessments of left ventricular systolic function were obtained at rest and during the four exercise tolerance trials in ten patients. At rest there was no difference in EDCA, ESCA, ESTA or ESMA (Table V-6) and resting FAC averaged ~55% with all gas mixtures. Additionally, LV end systolic transmural pressure and LV wall stress were also unchanged between conditions. In the transition from rest to exercise, EDCA significantly increased from resting values with all three experimental gas mixtures but not air (Figure V-11). In contrast, ESCA, ESTA and ESMA were unchanged from resting values in all conditions, while FAC increased to approximately 64% independent of gas mixture.

During exercise, EDCA was not different from air with HOX or HE-OX. However, a significant augmentation of EDCA was observed with HE-HOX (17.4 vs. 18.9 cm^3 in air and HE-HOX, respectively). ESCA, ESTA, ESMA, SA, LV end systolic transmural pressure, LV wall stress and LV contractility were also similar independent of gas.

Similar to the cardiac area changes observed during exercise, LVEDV was higher during exercise breathing HE-HOX compared to air (Table V-6). However, even though ejection fraction was similar between all gas mixtures (~70%), the increase in LVEDV with HE-HOX did not translate into a statistically significant improvement in stroke volume. However, the 6 ± 13%, 8 ± 17% and 12 ± 19% increase in SV with HOX, HE-OX and HE-HOX, respectively, is likely a physiologically important finding. Resting heart rates and the heart rate response to exercise are presented in Figure V-12. Heart rate was unchanged at rest but was significantly lower during exercise with HOX and the two helium gas mixtures. Even with this reduction in heart rate, cardiac output was unchanged from breathing air owing to the trend toward a greater stroke volume with each gas. (Figure V-12).

Correlations of Improved Exercise Tolerance

No significant relationship was found between any of the cardiovascular parameters measured and the increase in exercise time with each experimental gas. Furthermore, no significant correlations were observed between any measurements made in this study and the change in endurance time with HOX. However, due to the small sample size, the lack of significant correlations with HOX was believed to be due to one individual who stopped exercise prematurely as he lost control of the mouthpiece. After repeating the analysis without this outlier, significant correlations were observed between the improved endurance time with HOX and the reductions in V_E (r = -0.82) and breathing frequency (r = -0.67). Improvements in exercise time with HE-OX (Figure V-13) correlated best with the changes in peak inspiratory flow (r = 0.93), EELV expressed as a percent of TLC (r = -0.93), inspiratory capacity (r = 0.89), respiratory rate (r = -0.88) the total work of breathing per minute (r = -0.85) and peak P_{es} on expiration (r = -0.84). Interestingly, no relationship was observed between the improvement in maximal V_E with HE-OX and the improvements in endurance time (r = 0.10, p = 0.79). Stepwise multiple regression analysis demonstrated that the combination of improved peak inspiratory flow, EELV as a %TLC and the reduction in the total work of breathing explained 99% of the variance in improved endurance time with HE-OX ($r^2 = 0.99$, $p<0.0001$).

In a similar fashion, the improvements in endurance time with HE-HOX were also associated with a reduction in the work of breathing and improved inspiratory flow rates (Figure V-14). The best correlates of improved exercise time with HE-HOX were the changes in total elastic work of breathing per minute (r = -0.87), the total inspiratory resistive work of breathing per minute (r = -0.83), peak inspiratory (r = 0.82) and peak expiratory flow rates (r = -0.81) and mean expiratory flow rate (r = -0.79). In addition, significant correlations were also observed for the reduction in V_E (r = -0.71) and respiratory rate (r = 0.68) with HE-HOX. Stepwise multiple regression analysis of these variables, demonstrated that the reduction in the total elastic work of breathing with HE-HOX explained 75% of the variance in exercise time. The favorable reductions in mean expiratory flow rate then added approximately 7% to the explained variance (r^2 =0 .83, p <0.01).

Correlations of Improved Exertional Dyspnea.

No significant relationship existed between operational lung volumes during exercise and the level of exertional dyspnea experienced by participants during the air trial. However, there were significant relationships between dyspnea and both the resistive inspiratory work performed per minute (r = 0.84, p=0.008) and the total work of breathing (r = 0.71, p = 0.048). A similar but stronger correlation was also observed between the resistive work of breathing and dyspnea in the HOX trial (r = .91, p = 0.002). Furthermore, when the ratings of dyspnea at isotime 2 were combined for all gas mixtures (40 observations), it was found that the resistive (r = 0.66, p<0.0001) and total work performed in a minute (r = 0.58, p<0.001) were the best correlates of dyspnea.

Regression analysis was also performed to investigate the best correlates of improved dyspnea when breathing the three experimental gas mixtures. A significant relationship (r = -0.73, p = 0.016) was found between the changes in tidal volume and improved dyspnea with HOX, such that those with the greatest increases in tidal volume also had the greatest reductions in perceived dyspnea. Concomitant, the tidal volume to inspiratory capacity ratio (V_T/IC), which is a marker of mechanical constraint to tidal volume expansion (O'Donnell et al., 2001a), was also a significant predictor of the changes in dyspnea (r = -0.70, p=0.025). The improved ratings of exertional dyspnea with HE-OX were also related to improved lung volumes as significant correlations were observed between IC (r = -0.69, p = 0.027), EELV as a percentage of TLC (r = 0.71, p = 0.02), and tidal volume (-0.66, p = 0.039). Similar to the findings in HOX, the best correlate of the reduced dyspnea in HE-HOX was the V_T/IC ratio (r=-.77, p = 0.009), such that those who had the biggest reductions in ventilatory constraints had the biggest improvements in dyspnea. However, in contrast, a positive correlation was also found with IRV (r = 70, p = 0.024), in that those who did not have an improved IRV with HE-HOX had the greatest reductions in dyspnea.

Correlations of Cardiovascular Function

The enhanced left ventricular end diastolic cavity area with HE-HOX was best correlated with inspiratory capacity (r = 0.73), such that those with the greatest IC also had the largest EDCA during exercise. Significant correlations were also observed between EDCA and PEEPi (r = -0.68) as well as EDCA and EELV as a percentage of TLC (r = -0.69). Stepwise multiple regression analysis of these variables, demonstrated that the combination of IC and PEEPi explained 81% of the variance in left ventricular EDCA with the HE-HOX gas (r^2 =0 .81, p = 0.006).

Discussion

This is the first study to investigate the effects of helium-hyperoxia on pulmonary mechanics; cardiovascular function and exercise tolerance in COPD patients. The principle findings of this study were threefold and supplied evidence that supported all three of our hypotheses. Firstly, helium-hyperoxia improved exercise tolerance to a greater extent than any other gas mixture. Secondly, HE-HOX had a greater effect on dynamic hyperinflation, exertional dyspnea and the work of breathing than HOX or HE-OX. Finally, HE-HOX also increased LV end diastolic cavity area compared to breathing air, which appears to provide evidence that a reduction in dynamic hyperinflation can enhance LV diastolic filling.

Symptom Limited Exercise Tolerance

Hyperoxia and normoxic-helium significantly improved the exercise tolerance of COPD patients compared to air. Furthermore, the combination of the two gas mixtures had an additional effect on exercise time as subjects managed to perform 54 ± 56 and 92 ± 116% more work, than in either the HOX or HE-OX trials, respectively. At symptom limitation with air, the majority of subjects terminated exercise primarily due to severe dyspnea. Conversely, leg discomfort was the principal reason for stopping exercise with HE-HOX. This change in the symptoms responsible for limiting exercise, demonstrates that HE-HOX may reduce the ventilatory constraints associated with COPD to an extent that peripheral muscle function becomes the limiting factor in governing exercise capacity.

Ventilatory and Operational Lung Volume Responses to Exercise

Ventilation increased rapidly from rest when breathing air and by the first isotime had already reached 89% of peak values. Even at this initial isotime there was evidence of a significant constraint to V_E as expiratory flow limitation was present across a wide portion of tidal breathing (Figure V-9). As a result, EELV and EILV were elevated and tidal volume expansion was constrained from isotime one onwards. At normoxic symptom limitation the degree of dynamic hyperinflation averaged 0.43 ± 0.18 L and ranged from 0.17 L to 0.69 L. Moreover, EILV reached 94% of TLC, which is similar to the findings of O'Donnell et al., (2001a) and demonstrates the considerable flow limitation present in our subjects.

Breathing hyperoxia significantly reduced V_E throughout exercise, primarily through a reduction in breathing frequency. This attenuated ventilatory demand with hyperoxia is well documented (Dean et al., 1992; O'Donnell et al., 1997, 2001b; Somfay et al., 2001) and has consistently been attributed to a reduced chemoreceptor drive (Dean 1992 and O'Donnell et al., 1997). As a result of the reduced V_E with HOX, expiratory flow rate was decreased, which maintained lung volumes further to the right in the maximal flow volume envelope and delayed the progression of expiratory flow limitation (Figure V-9). As ventilatory demand increased with exercise duration, a greater expiratory flow limitation occurred and EELV rose in an attempt to increase expiratory flow rates. As hyperoxia does not affect the maximal flow volume loop (Figure V-8), expiratory flow limitation, the extent of dynamic hyperinflation, V_E and tidal volume were all unchanged from breathing air at symptom limitation. This finding has previously been reported by O'Donnell et al., (2001), and indicates that the ventilatory constraints to exercise are delayed with hyperoxia but not improved.

Unlike hyperoxia, previous studies have reported that breathing a normoxic-helium gas mixtures can increases V_E during exercise in healthy individuals with expiratory flow limitation (Ward et al., 1982; McCaran et al., 1998,1999; Babb, 1997) and COPD patients (Oelberg et al., 1998; Richardson et al., 1999). In the present study V_E was increased 16 ± 21% with HE-OX, which is comparable to that reported by others (Babb, 1997; Esposito and Ferretti, 1997). It is still unclear what precise mechanism(s) are responsible for the improved V_E with helium gas mixtures; however, evidence exists for both a reduction in pulmonary resistance (Babb, 2001) and reduced expiratory flow limitation (McClaran et al., 1999). As demonstrated in Figure V-8, HE-OX increased the maximal flow volume loop and reduced expiratory flow limitation. This reduction in ventilatory constraint increased expiratory flow rates and decreased dynamic hyperinflation as demonstrated by a significantly greater IC. However, the reductions in EELV with HE-OX were not accompanied by a decrease in EILV and as a result tidal volume was greatly improved at both isotimes one and two, even though V_E was unchanged from breathing air. At end exercise, the 0.21 L increase in tidal volume was totally responsible for the increase in V_E as breathing frequency was similar between the HE-OX and air trials.

There were highly variable individual responses to breathing HE-OX observed at exercise limitation, as V_E ranged from a decrease of 1.8 $L \cdot min^{-1}$ to an increase of 25.8 $L \cdot min^{-1}$. This finding was strongly correlated with FEV_1 and FEV_1 as a percentage of predicted, which suggests that there is a relationship between the level of airway obstruction and the change in V_E with HE-OX. However, this finding is in opposition to other studies that have reported similar proportional increases in V_E in individuals with vastly different pulmonary functions (Oelberg et al., 1998; McClaran et al., 1999). It is also interesting that no relationship was found between the improved V_E with HE-OX and the increase in endurance time with this gas. This finding suggests that the beneficial effects of HE-OX for enhancing V_E may not be as important as the benefits of this gas on operational lung volumes and dyspnea for improving exercise tolerance.

At end exercise with HE-OX, T_I/T_{TOT} was significantly reduced while peak inspiratory flow rates were enhanced. To achieve this breathing pattern with air, a much greater inspiratory pressure generation would be needed. However, due to the resistive unloading with HE-OX, the peak inspiratory esophageal pressures observed at symptom limitation were reduced compared to air ($p<0.05$). This ability to increase inspiratory flow rate, preserves expiratory time and when combined with an improved expiratory flow rate, maintains EELV closer to relaxation volume. As a result, dynamic hyperinflation and dyspnea are reduced. This observation would appear to explain why the improved peak inspiratory flow rates with HE-OX, combined with the reduced EELV as a percentage of TLC, collectively explain the improved exercise time with this gas.

The ventilatory response to exercise with HE-HOX was similar to HOX, with V_E and breathing frequency being reduced throughout exercise. However, unlike the HOX trial, tidal volume was enhanced at isotime two due to a greater improvement in IC ($r = 0.78$, $p = 0.01$). The mechanism responsible for this improved IC is similar to HOX, where reduced expiratory flow rates maintain EELV at a lower percentage of TLC. However, in addition to the reduction in expiratory flow rate, expiratory time was also significantly enhanced, further reducing EELV and augmenting tidal volume, which appears to be an attribute of the helium gas. A similar finding was also observed at symptom limitation, where tidal volume was enhanced with HE-HOX even though V_E was unchanged. At this time point IC was not different from air and unlike HE-OX, the mean and peak expiratory flow rates were not improved. Instead, the improved tidal volume was again related to the slight, but non-significant, increase in expiratory time ($r = 0.65$, $p = 0.04$), which maintained a more efficient breathing pattern by allowing patients more time to exhale.

HE-HOX had a significantly greater effect on dynamic hyperinflation, as both the absolute increase in EELV and the rate of dynamic hyperinflation were reduced compared to both HOX and HE-OX. However, at symptom limitation IC, IRV, dynamic hyperinflation and dyspnea were all similar to end exercise in the air trial, even though the maximal flow-volume loop was enhanced (Figure V-8). These findings raise two questions: firstly, at end exercise with HE-HOX had patients truly reached their ventilatory limitation or if they were able to tolerate more exercise could they have utilized the benefits of the helium gas to increase V_E further? Secondly, if mechanical constraint to ventilation was not the primary limitation for terminating exercise, as seven out of ten participants stopped due to leg fatigue, what mechanism is responsible for the skeletal muscle limitation? This second question is especially interesting, as end exercise S_PO_2 was unchanged from resting levels, suggesting that the content of arterial oxygen and likely O_2 delivery were maintained with HE-HOX.

Work of Breathing Responses to Exercise Breathing Helium-Oxygen Gases

Recently, helium-oxygen mixtures have been administered to individuals with COPD, to reduce the work of breathing associated with non-invasive ventilation (Jolliet et al., 1999, Jaber et al., 2000, Gainnier et al., 2003) and to reduce inspiratory muscle work in the postextubation period (Jaber et al., 2001). However, to our knowledge this is the first investigation to study the benefits of helium-oxygen gas mixtures on the work of breathing and exercise tolerance in COPD. At rest, the resistive work of breathing was significantly decreased with both helium gases and the elastic work of breathing was decreased with HOX and HE-HOX. As PEEPi was only present in four individuals during quiet breathing with air, the reduction in the elastic work of breathing was primarily due to the work done to overcome the elastic recoil of the lung. When the effect of breathing frequency was taken into account, the total work of breathing performed was only significantly different in the HE-HOX trial (161 vs. 283 L·cm H_2O^{-1}·min^{-1} in HE-HOX and air, respectively).

At the first isotime, the work to overcome airway resistance was reduced with all three experimental gas mixtures. The mechanisms responsible for this reduced resistive work is different between nitrogen and helium based gas mixtures. The lower density and slightly increased viscosity of helium, reduces airway resistance and the pressure needed to produce similar flow rates to air. In contrast, the physical properties of hyperoxia are comparable to air, and the reduction in the resistive work of breathing is due to the decreased expiratory flow rates that accompany the reduced ventilatory demand. The benefit of combining helium and hyperoxia was not noticeable at this first isotime as the resistive work of breathing was reduced to a similar extent in the HE-OX and HE-HOX trials. However, at the second isotime, the resistive work of breathing was significantly reduced only with HE-HOX, which demonstrates a cumulative advantage of this gas.

The helium hyperoxic gas mixture also had a superior effect on the elastic work of breathing because at isotime one only HE-HOX reduced both W_{IP} and W_{INP}. Instead, at the same isotime, only W_{INP} was reduced with HOX whereas only W_{IP} was decreased with HE-OX. The reduction in the W_{IP} with HE-OX was due to the significantly greater reduction in dynamic hyperinflation observed with this gas compared to HOX. The similar W_{INP} between the HE-OX and air trials was due to the enhanced tidal volume with HE-OX. Collectively, these findings resulted in a reduced total elastic work of breathing in only the HOX and HE-HOX trials at isotime one. However, the slight reduction in breathing frequency seen with HE-OX facilitated a decrease in the total elastic work of breathing per minute with this gas.

Similar to the resistive work of breathing, only HE-HOX had a significant effect on the work of breathing to overcome PEEPi at isotime two. W_{IP} was significantly reduced, due to the reduction in dynamic hyperinflation and concomitant PEEPi with HE-HOX. However, as with the HE-OX gas, W_{INP} was not affected by helium-hyperoxia due to the enhanced tidal volume. The finding that HE-HOX had a significantly greater effect on the resistive and elastic work of breathing than the other two gases is related to the ability of helium-hyperoxia to delay dynamic hyperinflation for longer. The improved IC observed with HE-HOX allowed lower expiratory flow rates to be utilized, which when combined with the physical properties of helium greatly reduces airway resistance. Additionally, the reduced EELV which occurred with HE-HOX, decreased the work needed to overcome lung compliance and PEEPi. Finally, as increased pressure generation and dynamic hyperinflation have both been implicated as mechanisms responsible for dyspnea in COPD patients (Killian and Jones 1988; Murciano et al., 2000; Diaz et al., 2000; Iandelli et al., 2002), it is not surprising that the reduced total elastic work of breathing was the best predictor of the improvements in exercise tolerance with this gas.

As a result of the aforementioned improvements in pulmonary mechanics, the total work of breathing was decreased with all three gas mixture at rest and isotime one, while only HE-HOX decreased the total work of breathing at isotime 2. As no known study has ever investigated the effects of HE-HOX on the work of breathing in COPD, we cannot compare our findings with any others. However, the finding of a reduced total work of breathing with HE-OX is different from Babb, (2001), who reported no effect of HE-OX on the total work of breathing at any time during a graded exercise test in individuals with mild chronic airflow limitation. These differences could be related to the individuals studied, as our subjects had moderate to severe COPD with a considerably greater level of airway obstruction than those in Babb's study (FEV_1/FVC 61% vs. 42%). Secondly, Babb (2001) does not report the presence of dynamic hyperinflation. If it did in fact occur in his subjects, it is reasonable to assume that it would be to a lesser extent than in a more severe COPD population. Therefore, the beneficial effect of reducing W_{IP} with HE-OX would not be reflected in the total elastic work reported by Babb (2001). A final difference between this investigation and that of Babb (2001), is that the present study did not match the external breathing circuit resistance between the helium and nitrogen based gases. It could be argued therefore, that the reduction in the total work of breathing found at isotimes one and two in our study represents a reduction in the resistance of the breathing circuit rather than being a "true" reduction in the work performed against the lung. However, before performing this study, pressure-flow characteristics of the apparatus used were measured and it was found that helium only reduced breathing circuit resistance at flow rates above 2.5 $L.s^{-1}$ (Figure V-15). As the mean expiratory flow rates in the HE-OX trial were below this value ($1.68L \cdot s^{-1}$) at peak exercise we argue that unloading of the breathing circuit resistance did not affect the findings of the present study. To further support this contention, the external resistance of the breathing circuit from peak expiratory mouth pressures and peak expiratory flow rates were calculated during each trial. Using this technique, no significant differences were observed between air and HE-OX at any time during exercise.

As previously mentioned, we found a significant relationship between the improved work of breathing and the greatly enhanced exercise time with HE-HOX. This relationship is likely due to the beneficial ability of this gas to attenuate dyspnea. However, another possible benefit of a reduced work of breathing may be a better distribution of cardiac output to the exercising muscles. Harms et al., (1997, 1998) demonstrated that in healthy athletic individuals ~ 16-18% of total cardiac output was required by the respiratory muscles and that reducing the work of breathing with a proportional assist ventilator increased blood flow to the muscles of locomotion. The increased work of breathing in COPD patients is estimated to govern as much as 35-50% of total body VO_2 (Levison and Cherniack, 1968), which would demand a much greater proportion of cardiac output. As cardiac output was unchanged with any gas mixture during exercise in this study, it is possible that the reduced work of breathing with HE-

HOX, allowed a greater portion of the available blood flow to be distributed to the legs, thereby improving O_2 supply, decreasing leg fatigue, and ultimately enhancing exercise tolerance. Additional support for this hypothesis can be ascertained by the highly significant correlation ($r = 0.92$) found between the reductions in dyspnea and the reductions in leg discomfort observed with HE-HOX in the present study.

The Effects of Helium and Oxygen on Cardiovascular Function

In COPD patients it is still unknown whether cardiovascular limitation plays a role in limiting exercise tolerance. A number of studies have reported an attenuated cardiac output at symptom limitation (Slutsky et al., 1981; Stewart and Lewis, 1986; Oelberg et al., 1998). However, whether this is truly a cardiovascular limitation or just a reflection of the pulmonary disorder prematurely terminating exercise has not been elucidated. During submaximal exercise, a normal cardiac output has often been reported (Light et al., 1984; Morrison et al., 1989). However, closer inspection often unveils an elevated heart rate with a concomitant reduction in stroke volume (Slutsky et al., 1981; Montes de Oca et al., 1986). In the absence of coronary artery disease, this abnormal stroke volume response to exercise is unlikely due to an intrinsic abnormality in LV contractility. Instead a number of studies have implicated the effect of dynamic hyperinflation as a possible mediator of this irregular LV response (Potter et al., 1971; Butler et al. 1988; Ranieri et al., 1996).

The presence of dynamic hyperinflation during exercise in COPD has been shown to increase cardiac fossa pressure (Butler et al., 1988), which may subsequently constrain the normal increases in cardiac volume needed to augment stroke volume during exercise. In addition, the large negative swings in pleural pressure required to overcome PEEPi, enhance RV preload (Mahler et al., 1984; Matthay et al., 1992) while adding to the already higher RV afterload (Ranieri et al., 1996). As a result, this increased right heart volume could decrease LV compliance through ventricular interaction (Jardin et al., 1984; Janicki and Weber, 1980). If this theory is correct, it is feasible that a reduction in dynamic hyperinflation would decrease the negative pleural pressure swings associated with overcoming PEEPi, while concomitantly reducing both the impedance to RV output and RV preload. This decrease in RV end diastolic volume could improve LV compliance by inducing a rightward septal shift. Although, this mechanism was not directly investigated, our findings do supply preliminary evidence to support the claim that reductions in dynamic hyperinflation can improve LV preload in COPD patients. We observed that breathing HE-HOX increased LV end diastolic cavity area compared to breathing air. Furthermore, the improvement in LV preload observed with HE-HOX was related to the superior reductions in dynamic hyperinflation with this gas, as EDCA correlated positively with IC and negatively with PEEPi.

Even though the reductions in dynamic hyperinflation appear to be related to the improvements in LV preload, it is possible that our findings may actually underestimate the beneficial effects of reduced dynamic hyperinflation on LV filling. All of our measurements of cardiovascular function were made around end expiration when the echocardiographic images were clearest. However, the real benefits of reducing dynamic hyperinflation on ventricular interaction and diastolic filling are more likely to occur during the inspiratory cycle, when the large negative swings in esophageal pressure would greatly increase RV preload and afterload. Furthermore, due to the design of the study the cardiovascular assessment was performed before the exercise tolerance trials, therefore the exact duration of exercise that participants could perform was unknown. As a result the echocardiographic assessment was performed quite early in exercise and the largest difference in cardiac function between the four gas mixtures may have been missed. For example, the reductions in heart rate at isotime two are much greater than at isotime one (Figure V-16). If cardiac output were still unchanged between conditions the stroke volume would be considerably higher with all three gas mixtures.

In addition to the finding of an improved LV end diastolic volume, we found no significant change in LV afterload measured by LV wall stress or LV contractility. As EF was also unchanged the increased LVEDV should increase LV stroke volume by benefit of the Frank-Starling mechanism. However, even though LV stroke volume increased 12 ± 19%, this finding did not achieve statistical significance ($p = 0.20$). The reason for this non-statistical finding is likely related to the small sample size used and the variability in exercise echocardiography measurement. However, these findings would still appear to support a beneficial role of reduced lung inflation on LV function and further investigation is now needed to substantiate these findings.

Limitations of the Study

One limitation of the present study that should be acknowledged is the possible inaccurate positioning of the static chest wall compliance line used to calculate the elastic work of breathing. As explained in Appendix B, the line is positioned assuming that end-expiratory lung volume during quiet breathing is an accurate representation of the relaxation volume and pressure of the respiratory system. However, this may not be accurate for two reasons. Firstly, as dynamic hyperinflation is often present in COPD patients at rest, EELV may actually be above relaxation volume even during quiet breathing. Secondly, at end expiration, continued expiratory muscle recruitment can artificial increase PEEPi above that due to dynamic hyperinflation, which would increase end-expiratory pressure independent of the chest wall elasticity. In combination, these findings would move point F in Figure B-2 upwards and to the right of the true relaxation volume. As a result the work needed to overcome PEEPi (W_{IP}) may be slightly overestimated

In the study of Sliwinski et al., (1998) this problem was corrected for by subtracting the expiratory rise in gastric pressures from the esophageal pressure at EELV. Unfortunately, as gastric pressures were not measured in the present study this was not done. However, two pieces of evidence that support the accuracy of our findings should be mentioned. The mean PEEPi observed in Sliwinski's study during quiet breathing was 2.5 cm H_2O and the correction for the five patients who contributed to this PEEPi was 2.1 cm H_2O. In our study, the mean PEEPi was only 0.7 cm H_2O at rest, if a similar amount of expiratory muscle recruitment is assumed for the four individuals that demonstrated PEEP in the present study, the correction factor would only be around 0.5 cm H_2O. Secondly, as there was no significant difference observed in EELV or PEEPi during quiet breathing with the four gas mixtures used in this study, the extent of error in W_{IP} is likely fairly consistent across each of the four conditions. Considering these two findings and the magnitude of the reduction in W_{IP} reported with the helium gas mixtures, it is believed that the slight overestimation in W_{IP} that may exist in this study will not affect the outcome of our findings.

Summary

In summary, the administration of a helium based hyperoxic gas mixture to individuals with moderate to severe COPD enhances exercise tolerance to a greater extent than either a normoxic-helium or a nitrogen-based hyperoxic gas. This improvement in exercise tolerance is combined with reduced exertional dyspnea and is related to additional improvements in both operational lung volumes and the work of breathing. Moreover, the greater reductions in dynamic hyperinflation seen with HE-HOX appear to also improve cardiovascular function, as a greater LV end diastolic cavity area was observed during exercise with this gas. Collectively, these three major findings have significant clinical implications for reducing dyspnea and improving the exercise tolerance of patients with COPD.

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Table V-1: Subject Characteristics and Pulmonary Function

	Value	%Pred
Age, yr	64 ± 11	
Height, cm	179 ± 5	
Mass, kg	82 ± 15	
Body Mass Index, kg/m^2	26 ± 4	
Pulmonary function and gas exchange		
FEV_1, L	1.64 ± 0.56	46 ± 16
FVC, L	3.83 ± 0.94	84 ± 20
FEV_1/FVC, %	42.3 ± 7.8	55 ± 10
TLC, L	9.23 ± 1.42	140 ± 23
RV, L	5.03 ±1.67	204 ± 71
FRC, L	6.06 ± 1.68	164 ± 49
IC, L	3.17 ± 0.92	
D_{LCO}, ml/min/mm Hg	18.7 ± 4.3	70 ± 16
S_{Raw}, cm H_2O/L/s	4.38 ± 0.22	
P_aO_2, mm Hg	69.5 ± 7.4	
P_aCO_2, mm Hg	36.7 ± 3.1	
pH	7.42 ± 0.02	
HCO_3	23.6 ± 14.7	
Hb	14.7 ± 1.2	
Hct	45.1 ± 0.5	

Abbreviations: FEV_1 = forced expired volume in one second, FVC = forced vital capacity, TLC – total lung capacity, RV = residual volume, FRC = functional residual capacity, IC = inspiratory capacity, D_{LCO} =diffusion capacity of the lung for carbon monoxide, S_{Raw} = specific airway resistance, P_aO_2 = partial pressure of arterial oxygen, P_aCO_2 = partial pressure of arterial carbon dioxide, HCO_3 = bicarbonate, Hb = hemoglobin concentration, Hct = hematocrit. Values are means ± SD, n=11.

Table V-2: Incremental Exercise Results on Room Air

	Value
VO_2, ml.kg^{-1}.min^{-1}	18.0 ± 4.9
VO_2, l.min^{-1}	1.47 ± 0.4
PO, W	115 ± 37
H_R,	130 ± 9.6
S_pO_2, %	89 ± 4.2
RER	1.05 ± 0.09
V_E, l.min^{-1}	57.3 ± 20.8
V_T, l	1.75 ± 0.5
f	33 ± 9
Dyspnea	6.4 ± 2.1
Leg Fatigue	5.2 ± 2.0
Reason for stopping (n=11)	
Dyspnea	5
Leg Fatigue	2
Both	4

Abbreviations: VO_2 = oxygen consumption, PO = power output, H_R = heart rate, S_PO_2 = oxyhemoglobin saturation, RER = respiratory exchange ratio, V_E = ventilation, V_T = tidal volume, f = breathing frequency.

Values are means ± SD, n=11.

Table V-3: Operational Lung Volume Responses to Exercise

	AIR	HOX	HE-OX	HE-HOX
Rest				
IC, L	2.64 ± 0.88	2.65 ± 0.84	2.71 ± 0.88	2.74 ± 1.42
IRV, L	1.48 ± 0.60	1.55 ± 0.73	1.54 ± 0.80	1.59 ± 0.55
EILV, %TLC	84.1 ± 5.7	83.3 ± 7.2	83.4 ± 7.72	82.8 ± 5.24
EILV, L	7.76 ± 1.30	7.68 ± 1.33	7.69 ± 1.34	7.65 ± 1.33
EELV, %TLC	71.1 ± 9.5	70.8 ± 9.5	70.1 ± 9.9	69.8 ± 9.8
EELV	6.59 ± 1.54	6.58 ± 1.58	6.52 ± 1.61	6.49 ± 1.63
Isotime One				
IC, L	2.26 ± 0.86^{bcd}	2.40 ± 0.84^{ad}	2.50 ± 0.84^{a}	2.55 ± 0.85^{ab}
IRV, L	0.62 ± 0.63^{d}	0.73 ± 0.50	0.69 ± 0.55	0.82 ± 0.57^{a}
DH, L	$0.38 \pm 0.19^{c,d}$	0.25 ± 0.17	0.21 ± 0.24^{a}	0.20 ± 0.21^{a}
EILV, %TLC	93.3 ± 6.19^{d}	92.0 ± 5.12	92.8 ± 5.3	91.3 ± 5.6^{a}
EILV, L	8.61 ± 1.44^{d}	8.50 ± 1.45	8.55 ± 1.32	8.42 ± 1.35^{a}
EELV, %TLC	75.0 ± 9.4^{bcd}	73.4 ± 9.3^{ad}	72.3 ± 9.7^{a}	$71.8 \pm 9.9^{a,b}$
EELV, L	6.97 ± 1.66^{bcd}	6.83 ± 1.69^{ad}	6.73 ± 1.68^{a}	$6.69 \pm 1.69^{a,b}$
Isotime Two				
IC, L	2.24 ± 0.91^{cd}	2.39 ± 0.85	2.51 ± 0.85^{a}	2.54 ± 0.90^{a}
IRV, L	0.56 ± 0.39	0.67 ± 0.40	0.60 ± 0.48	0.68 ± 0.49
DH, L	0.43 ± 0.18	0.30 ± 0.20^{a}	0.26 ± 0.22^{a}	0.24 ± 0.19^{a}
EILV, %TLC	93.9 ± 3.8	92.7 ± 3.78	93.4 ± 4.68	92.5 ± 4.89
EILV, L	8.49 ± 1.28	8.37 ± 1.24	8.44 ± 1.28	8.36 ± 1.28
EELV, %TLC	74.9 ± 9.6^{cd}	73.1 ± 9.3	71.8 ± 9.569^{a}	71.5 ± 10.069^{a}
EELV, L	6.80 ± 1.53^{cd}	6.65 ± 1.53	6.54 ± 1.57^{a}	6.51 ± 1.61^{a}

Table V-3: Operational Lung Volume Responses to Exercise (Continued)

Parameters	NOX	HOX	HE-OX	HE-HOX
Isotime Three				
IC, L		2.27 ± 0.82^{d}		2.45 ± 0.85^{b}
IRV, L		0.53 ± 0.25		0.60 ± 0.27
DH, L		0.42 ± 0.19		0.33 ± 0.27
EILV, %TLC		94.2 ± 2.4		93.4 ± 2.7
EILV, L		8.52 ± 1.26		8.45 ± 1.30
EELV, %TLC		74.6 ± 8.8^{d}		72.4 ± 2.7^{b}
EELV, L		6.78 ± 1.50^{d}		6.60 ± 1.62^{b}
End Exercise				
IC, L	2.24 ± 0.91	2.27 ± 0.82	2.40 ± 0.80	2.35 ± 0.85
IRV, L	0.56 ± 0.39	0.53 ± 0.29	0.51 ± 0.24	0.51 ± 0.26
DH, L	0.43 ± 0.18	0.42 ± 0.19	0.36 ± 0.23	0.43 ± 0.20
EILV, %TLC	93.9 ± 3.8	94.1 ± 2.88	94.4 ± 2.54	94.4 ± 2.67
EILV, L	8.49 ± 1.28	8.51 ± 1.29	8.54 ± 1.29	8.54 ± 1.32
EELV, %TLC	74.9 ± 9.6	74.6 ± 8.8	73.0 ± 9.1	73.5 ± 9.72
EELV, L	6.80 ± 1.53	6.77 ± 1.49	6.64 ± 1.54	6.69 ± 1.61

Abbreviations: IC = Inspiratory capacity, IRV = inspiratory reserve volume, DH = dynamic hyperinflation, EILV = end inspiratory lung volume, EELV = end expiratory lung volume, %TLC = total lung capacity. Values are means ± SD, n=11. For a explanation of the three isotimes please see text, a = $p<0.05$ vs. AIR, b = $p<0.05$ vs. HOX; c = $p<0.05$ vs. HE-OX; d = $p<0.05$ vs. HE-HOX

Table V-4: Work of Breathing Responses to Exercise

	AIR	HOX	HE-OX	HE-HOX
Rest				
W_R, L/cm H_2O	5.6 ± 1.5^{cd}	4.9 ± 2.9	3.6 ± 1.7^{a}	3.5 ± 1.8^{a}
W_{RTOTAL}/min, L/cm H_2O/min	79.9 ± 21.4^{d}	71.5 ± 39.7^{a}	57.7 ± 48.3	51.4 ± 29.6^{a}
W_{INP}, L/cm H_2O	12.8 ± 6.5^{bd}	8.9 ± 4.8^{a}	10.9 ± 8.4	8.1 ± 4.1^{a}
W_{IP}, L/cm H_2O	1.1 ± 1.3	0.64 ± 0.93	0.42 ± 0.9	0.30 ± 0.72
W_{ITOTAL}, L/cm H_2O	13.9 ± 6.4^{bd}	9.5 ± 4.6^{a}	11.3 ± 8.1	8.4 ± 4.1^{a}
W_{ITOTAL}/min, L/cm H_2O/min	194 ± 80^{d}	139 ± 67	153 ± 81	112 ± 41.9^{a}
W_{Ex}, L/cm H_2O	0.64 ± 0.84	0.35 ± 0.55	0.18 ± 0.23	0.20 ± 0.21
W_{TOTAL}, L/cm H_2O	20.1 ± 6.04^{bd}	14.7 ± 6.0^{a}	15.1 ± 8.6	12.1 ± 4.2^{a}
W_{TOTAL} /min, L/cm H_2O/min	283 ± 78^{d}	215 ± 74	213 ± 105	166 ± 53^{a}
Isotime One				
W_R, L/cm H_2O	15.4 ± 7.1^{abc}	11.1 ± 6.4^{a}	9.5 ± 1.8^{a}	9.5 ± 4.1^{a}
W_{RTOTAL}/min, L/cm H_2O/min	432 ± 210^{bcd}	255 ± 118^{a}	246 ± 92^{a}	223 ± 89^{a}
W_{INP}, L/cm H_2O	25.9±13.0^{b}	19.1 ± 8.5^{a}	23.1 ± 11.9	21.7 ± 9.1
W_{IP}, L/cm H_2O	7.2 ± 2.9^{c,d}	5.5 ± 2.1^{c,d}	3.5 ± 2.9^{a,b}	3.1 ± 2.8^{a,b}
W_{ITOTAL}, L/cm H_2O	33.1 ± 13.8^{bd}	24.6 ± 8.1^{a}	26.7 ± 11.1	24.8 ± 8.7^{a}
W_{ITOTAL}/min, L/cm H_2O/min	950 ± 505^{bcd}	600 ± 271^{a}	721 ± 456^{a}	593 ± 265^{a}
W_{Ex}, L/cm H_2O	4.9 ± 5.9^{c}	2.4 ± 2.2	0.83 ± 0.82^{a}	1.6 ± 1.7
W_{TOTAL}, L/cm H_2O	53 ± 21^{abc}	38.1 ± 11.6^{a}	36.9 ± 12.0^{a}	35.9 ± 9.9^{a}
W_{TOTAL} /min, L/cm H_2O/min	1527 ± 779^{abc}	913 ± 311^{a}	990 ± 536^{a}	852 ± 290^{a}
Isotime Two				
W_R, L/cm H_2O	15.8 ± 7.4^{d}	12.8 ± 7.2	14.2 ± 9.4	10.0 ± 4.1^{a}
W_{RTOTAL}/min, L/cm H_2O/min	474 ± 222^{d}	292 ± 119^{a}	396 ± 268	228 ± 85^{a}
W_{INP}, L/cm H_2O	26.7 ± 12.9	21.7 ± 10.3	28.5 ± 12.4	23.7 ± 8.5
W_{IP}, L/cm H_2O	7.7 ± 1.9^{d}	6.1 ± 2.3	5.7 ± 3.1	3.6 ± 2.1^{a}
W_{ITOTAL}, L/cm H_2O	34.5 ± 13.2	27.8 ± 9.5	34 ± 12	27.3 ± 2.1
W_{ITOTAL}/min, L/cm H_2O/min	1121 ± 680^{bd}	693 ± 313^{a}	978 ± 478	661 ± 300^{a}
W_{Ex}, L/cm H_2O	7.4 ± 2.2	6.1 ± 2.3	2.8 ± 3.1	3.6 ± 2.1
W_{TOTAL}, L/cm H_2O	57.7±21.8^{bd}	43.7 ± 14.2^{a}	51.3 ± 23.0	39.6 ± 8.4^{a}
W_{TOTAL} /min, L/cm H_2O/min	1938 ± 1457^{d}	1060 ± 354	1442 ± 742	940 ± 317^{a}

Table V-4: Work of Breathing Responses to Exercise (Continued)

	AIR	HOX	HE-OX	HE-HOX
Isotime Three				
W_R, L/cm H_2O		14.4 ± 3.7		12.4 ± 8.1
W_R, L/cm H_2O/min		423 ± 174		303 ± 130
W_{INP}, L/cm H_2O		22.2 ± 8.3		23.3 ± 10.2
W_{IP}, L/cm H_2O		7.4 ± 2.0		6.4 ± 3.2
W_{ITOTAL}, L/cm H_2O		29.6 ± 11.3		29.7 ± 10.2
W_{ITOTAL}/min, L/cm H_2O/min		925 ± 507		812 ± 397
W_{Ex}, L/cm H_2O		4.9 ± 6.4		2.3 ± 2.7
W_{TOTAL}, L/cm H_2O		48.9 ± 12.2		44.5 ± 16.5
W_{TOTAL} /min, L/cm H_2O/min		1541 ± 946		1178 ± 463
End Exercise				
W_R, L/cm H_2O	15.8 ± 7.4	14.6 ± 3.5	15.4 ± 8.6	13.4 ± 7.9
W_{RTOTAL}/min, L/cm H_2O/min	474 ± 222	428 ± 171	477 ± 251	362 ± 149
W_{INP}, L/cm H_2O	26.7 ± 12.9	22.2 ± 8.3	27.4 ± 12.5	26.0 ± 12.1
W_{IP}, L/cm H_2O	7.7 ± 1.9	7.7 ± 2.3	6.6 ± 2.4	6.6 ± 3.1
W_{ITOTAL}, L/cm H_2O	34.5 ± 13.2	29.9 ± 11.1	34.0 ± 12.7	32.6 ± 11.2
W_{ITOTAL}/min, L/cm H_2O/min	1121 ± 680	932 ± 502	1122 ± 583	995 ± 576
W_{Ex}, L/cm H_2O	7.4 ± 2.2	5.1 ± 6.4	3.3 ± 3.6	3.4 ± 4.2
W_{TOTAL}, L/cm H_2O	57.7 ± 21.8	49.6 ± 11.8	52.7 ± 23.9	49 ± 18
W_{TOTAL} /min, L/cm H_2O/min	1938 ± 1457	1559 ± 937	1714 ± 91	1464 ± 745

Abbreviations: W_R = Resistive work, W_{INP} = elastic work on inspiration to overcome the elastic recoil of the lung or the "non PEEPi" load, W_{IP} = elastic work of inspiration to overcome PEEPi, W_{Ex} = Additional work performed by the respiratory muscles on expiration, W_{ITOTAL}= total inspiratory work, W_{TOTAL} = Total work of breathing. Values are means ± SD, n=9. For a description of the three isotimes please see text, a = $p<0.05$ vs. AIR, b = $p<0.05$ vs. HOX; c = $p<0.05$ vs. HE-OX; d = $p<0.05$ vs. HE-HOX

Table V-5: Pressure, Flow and Symptom Responses to Exercise

	AIR	HOX	HE-OX	HE-HOX
Rest				
Peak Exp P_{es}, cm H_2O	2.8 ± 3.8	2.6 ± 3.4	1.2 ± 2.8	0.9 ± 2.2
Peak Ins P_{es}, cm H_2O	-11.9 ± 3.9	-10.4 ± 3.6	-10.3 ± 4.1	-10.5 ± 4.9
PEF, $L.s^{-1}$	1.35 ± 0.45	1.09 ± 0.46	1.24 ± 0.35	1.10 ± 0.43
MEF, $L.s^{-1}$	0.65 ± 0.22	0.53 ± 0.17	0.63 ± 0.18	0.56 ± 0.22
PIF, $L.s^{-1}$	-1.39 ± 0.22	-1.26 ± 0.38	-1.37 ± 0.87	-1.27 ± 0.39
MIF, $L.s^{-1}$	-1.35 ± 0.90	-0.91 ± 0.32	-1.03 ± 0.25	-1.10 ± 0.40
Isotime One				
Peak Exp P_{es}, cm H_2O	$14.5 \pm 12.1^{c,d}$	10.0 ± 5.5	7.5 ± 5.0^{a}	7.46 ± 2.94^{a}
Peak Ins P_{es}, cm H_2O	-18.4 ± 5.6^{bcd}	-16.1 ± 4.0^{a}	-14.1 ± 5.1^{a}	-14.2 ± 5.1^{a}
PEF, $L.s^{-1}$	2.76 ± 1.20^{bd}	2.05 ± 0.59^{ac}	2.76 ± 1.01^{bd}	2.19 ± 0.64^{ac}
MEF, $L.s^{-1}$	1.45 ± 0.59^{b}	1.18 ± 0.34^{ac}	1.55 ± 0.56^{bd}	1.26 ± 0.39^{c}
PIF, $L.s^{-1}$	-3.05 ± 0.90^{b}	-2.38 ± 0.46^{ac}	-3.00 ± 0.85^{b}	-2.59 ± 0.65
MIF, $L.s^{-1}$	-2.17 ± 0.74^{b}	-1.79 ± 0.41^{ac}	-2.30 ± 1.14^{bd}	-1.94 ± 0.50^{c}
Dyspnea	3.6 ± 0.74^{bcd}	2.2 ± 0.8^{a}	2.3 ± 1.14^{a}	1.5 ± 1.1^{ac}
Leg Fatigue	3.1 ± 1.50^{bd}	2.2 ± 1.6^{a}	2.5 ± 1.61	2.0 ± 1.5^{a}
Isotime Two				
Peak Exp P_{es}, cm H_2O	18.0 ± 18.6	10.7 ± 7.0	7.7 ± 5.50	8.9 ± 4.1
Peak Ins P_{es}, cm H_2O	-19.9 ± 5.8^{bcd}	-16.0 ± 4.5^{a}	-15.8 ± 4.42^{a}	-14.7 ± 5.2^{a}
PEF, $L.s^{-1}$	3.00 ± 1.40^{bd}	2.10 ± 0.63^{ac}	3.00 ± 1.04^{bd}	2.28 ± 0.63^{ac}
MEF, $L.s^{-1}$	1.53 ± 0.61^{b}	1.22 ± 0.36^{ac}	1.62 ± 0.59^{bd}	1.34 ± 0.41^{c}
PIF, $L.s^{-1}$	-3.16 ± 0.94^{bd}	-2.07 ± 1.10^{ac}	-3.17 ± 0.91^{bd}	-2.65 ± 0.62^{ac}
MIF, $L.s^{-1}$	-2.32 ± 0.79^{b}	-1.83 ± 0.37^{ac}	-2.37 ± 1.45^{b}	-2.00 ± 0.54
Dyspnea	5.8 ± 2.2^{bcd}	2.7 ± 0.9^{a}	3.1 ± 1.1^{a}	1.9 ± 1.4^{a}
Leg Fatigue	5.0 ± 1.6^{bd}	2.8 ± 1.6^{a}	3.6 ± 2.2^{d}	2.2 ± 1.5^{ac}

Table V-5: Pressure, Flow and Symptom Responses to Exercise (Continued)

Parameters	AIR	HOX	HE-OX	HE-HOX
Isotime Three				
Peak Exp P_{es}, cm H_2O		16.2 ± 15.0		12.0 ± 8.7
Peak Ins P_{es}, cm H_2O		-18.3 ± 3.9		-17.2 ± 6.1
PEF, $L.s^{-1}$		2.51 ± 1.11		2.76 ± 1.06
MEF, $L.s^{-1}$		1.35 ± 0.49		1.41 ± 0.42
PIF, $L.s^{-1}$		-2.71 ± 0.79		-2.97 ± 0.67
MIF, $L.s^{-1}$		-2.06 ± 0.54		-2.30 ± 0.76
Dyspnea		5.3 ± 2.0^{d}		3.7 ± 1.8^{b}
Leg Fatigue		5.1 ± 2.3		4.0 ± 2.2
End Exercise				
Peak Exp P_{es}, cm H_2O	18.0 ± 18.6	17.5 ± 14.6	10.8 ± 7.4	12.8 ± 8.1
Peak Ins P_{es}, cm H_2O	-19.9 ± 5.8^{c}	-18.6 ± 4.2	-16.4 ± 3.8^{a}	-18.1 ± 5.01
PEF, $L.s^{-1}$	3.00 ± 1.40	2.69 ± 1.15^{c}	3.46 ± 1.50^{bd}	2.61 ± 1.05^{c}
MEF, $L.s^{-1}$	1.53 ± 0.61	1.41 ± .49^{c}	1.68 ± 0.75^{b}	1.48 ± 0.51
PIF, $L.s^{-1}$	-3.16 ± 0.94^{c}	-2.69 ± 1.43^{c}	-3.83 ± 1.36^{abd}	-2.97 ± 0.68^{c}
MIF, $L.s^{-1}$	-2.32 ± 0.79	-2.22 ± 0.56^{c}	-2.73 ± ^{bd}	-2.28 ± 0.55^{c}
Dyspnea	5.8 ± 2.2^{c}	4.9 ± 2.6	4.9 ± 2.7^{a}	5.1 ± 2.1
Leg Fatigue	5.2 ± 1.8	5.2 ± 2.0	5.6 ± 1.7	5.6 ± 2.1
Reason For Stopping				
Dyspnea	7	4	3	2
Leg Fatigue	2	5	4	7
Both	1	0	2	0
Other	0	1	1	1

Abbreviations: Peak Exp P_{es} = Peak expiratory pressure during tidal breathing, Peak Ins P_{es} = Peak inspiratory pressure during tidal breathing , PEF = peak expiratory flow, MEF = mean expiratory flow, PIF = peak inspiratory flow, MIF = mean inspiratory flow. Values are means ± SD, n=9 for pressures and n=11 for flows and symptoms. For a description of the three isotimes please see text, a = $p<0.05$ vs. AIR, b = $p<0.05$ vs. HOX; c = $p<0.05$ vs. HE-OX; d = $p<0.05$ vs. HE-HOX

Table V-6: Cardiovascular Responses to Exercise

	AIR		HOX		HE-OX		HE-HOX	
	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
Heart Rate, beats.min^{-1}	83 ± 11	118 ± 13	83 ± 10	113 ± 11	84 ± 9	112 ± 10	82 ± 11	110 ± 11
SBP, mm Hg	119 ± 11	161 ± 16	121 ± 12	158 ±19	122 ± 13	156 ± 21	118 ± 11	156 ± 16
DBP, mm Hg	77 ± 11	82 ± 11	77 ± 9	80 ± 11	80 ± 8	79 ± 11	76 ± 6	76 ± 10
Areas (Left Ventricle)								
EDCA, cm^2	16.1 ± 2.4	17.4 ± 2.6	16.0 ± 2.5	18.6 ± 3.2	15.6 ± 3.3	18.3 ± 2.3	16.2 ± 3.1	18.9 ± 2.4*
ESCA, cm^2	7.3 ± 2.0	6.3 ± 1.4	7.3 ± 2.0	6.9 ± 1.4	7.0 ± 1.9	6.5 ± 1.4	7.1 ± 1.8	6.8 ± 1.6
ESTA, cm^2	22.9 ± 3.8	22.1 ± 3.3	23.4 ± 3.8	21.7 ± 2.9	22.7 ± 3.5	21.9 ± 3.2	22.9 ± 3.7	22.9 ± 2.9
ESMA, cm^2	15.6 ± 2.4	15.8 ± 2.2	16.2 ± 3.1	15.6 ± 2.6	15.7 ± 2.5	15.5 ± 3.3	16.0 ± 2.7	16.1 ± 2.6
SA, cm^2	8.8 ± 1.7	11.1 ± 2.1	8.7 ± 2.2	11.7 ± 2.4	8.6 ± 2.0	11.9 ± 2.4	9.1 ± 2.3	12.1 ± 2.2
Contractility, mm Hg.cm^2	17.5 ± 5.6	25.4 ± 5.4	18.4 ± 7.7	23.0 ± 6.5	18.7 ± 6.3	25.2 ± 7.3	17.7 ± 5.2	23.7 ± 7.0
FAC	0.55 ± 0.09	0.64 ± 0.06	0.55 ± 0.10	0.63 ± 0.05	0.55 ± 0.07	0.64 ± 0.08	0.56 ± 0.08	0.64 ± 0.07
Volumes (Left Ventricle)								
LVEDV, ml	94 ± 16	103 ± 18	93 ± 17	111 ± 22	90 ± 22	109 ± 16	95 ± 22	114 ± 16*
LVESV, ml	37 ± 12	30 ± 9	37 ± 12	34 ± 9	35 ± 12	32 ± 8	35 ± 11	34 ± 10
SV, ml	58 ± 12	73 ± 14	57 ± 15	77 ± 17	56 ± 14	78 ± 16	59 ± 16	80 ± 15
EF	0.61 ± 0.11	0.70 ± 0.06	0.61 ± 0.10	0.69 ± 0.05	0.62 ± 0.07	0.71 ± 0.08	0.63 ± 0.09	0.70 ± 0.07
Q, ml	4656 ± 1016	8653 ± 2226	4669 ± 1272	8687 ± 2311	4605 ± 973	8713 ± 1987	4727 ± 1083	8711 ± 1756
Pressures & Wall Stress								
LVESTMP, mm Hg	116 ± 12	149 ± 20	119 ± 13	149 ± 19	121 ± 13	150 ± 22	117 ± 12	150 ± 15
LVESWS, kilodyne/cm^2	73 ± 19	82 ± 21	73 ± 22	89 ± 18	72 ± 18	89 ± 25	70 ± 16	86 ± 22

Abbreviations: SBP = Systolic blood pressure, DBP = diastolic blood pressure, EDCA = end diastolic cavity area, ESCA = end systolic cavity area, ESTA = end systolic total cavity area, ESMA = end systolic myocardial area, SA =stroke Area, FAC = fractional area change, LVEDV = left ventricular end diastolic volume, LVESV = left ventricular end systolic volume, SV = stroke volume, Q = cardiac output. Values are means ± SD, n=10. * = significantly different from AIR

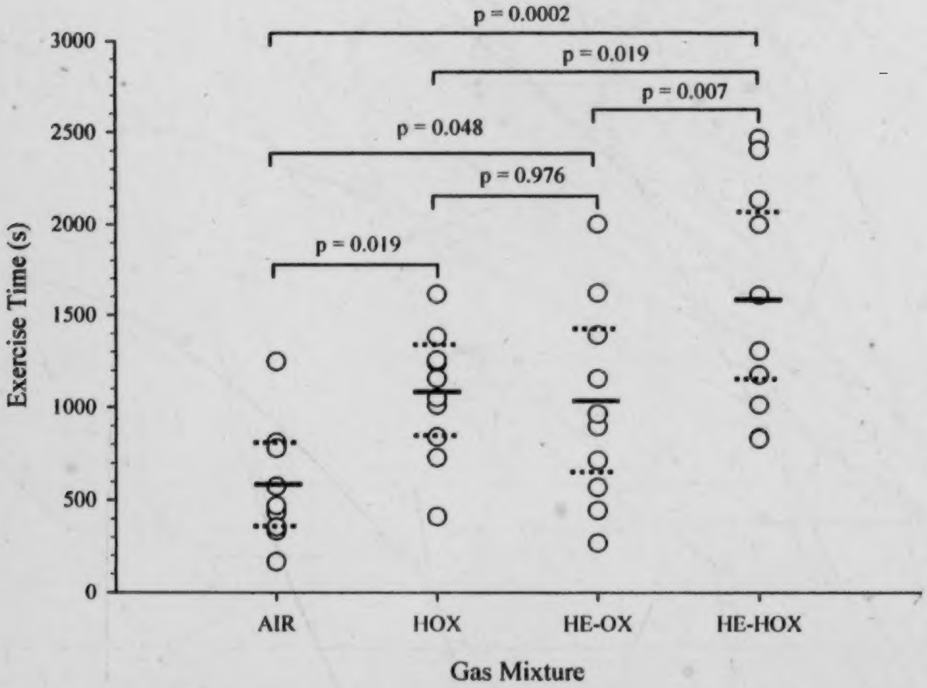

Figure V-1: The effect of each gas mixture on exercise tolerance. —— = mean values, ••••• = 95% confidence intervals. p values for each comparison are also presented.

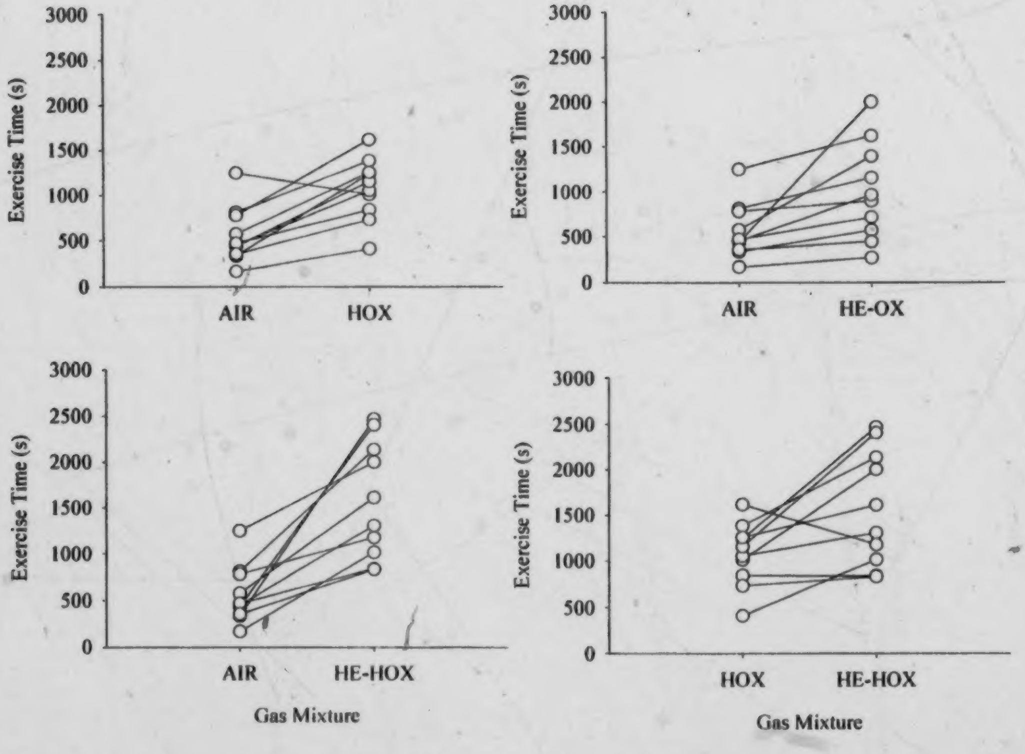

Figure V-2: Comparison of individual exercise responses to breathing the experimental gas mixtures.

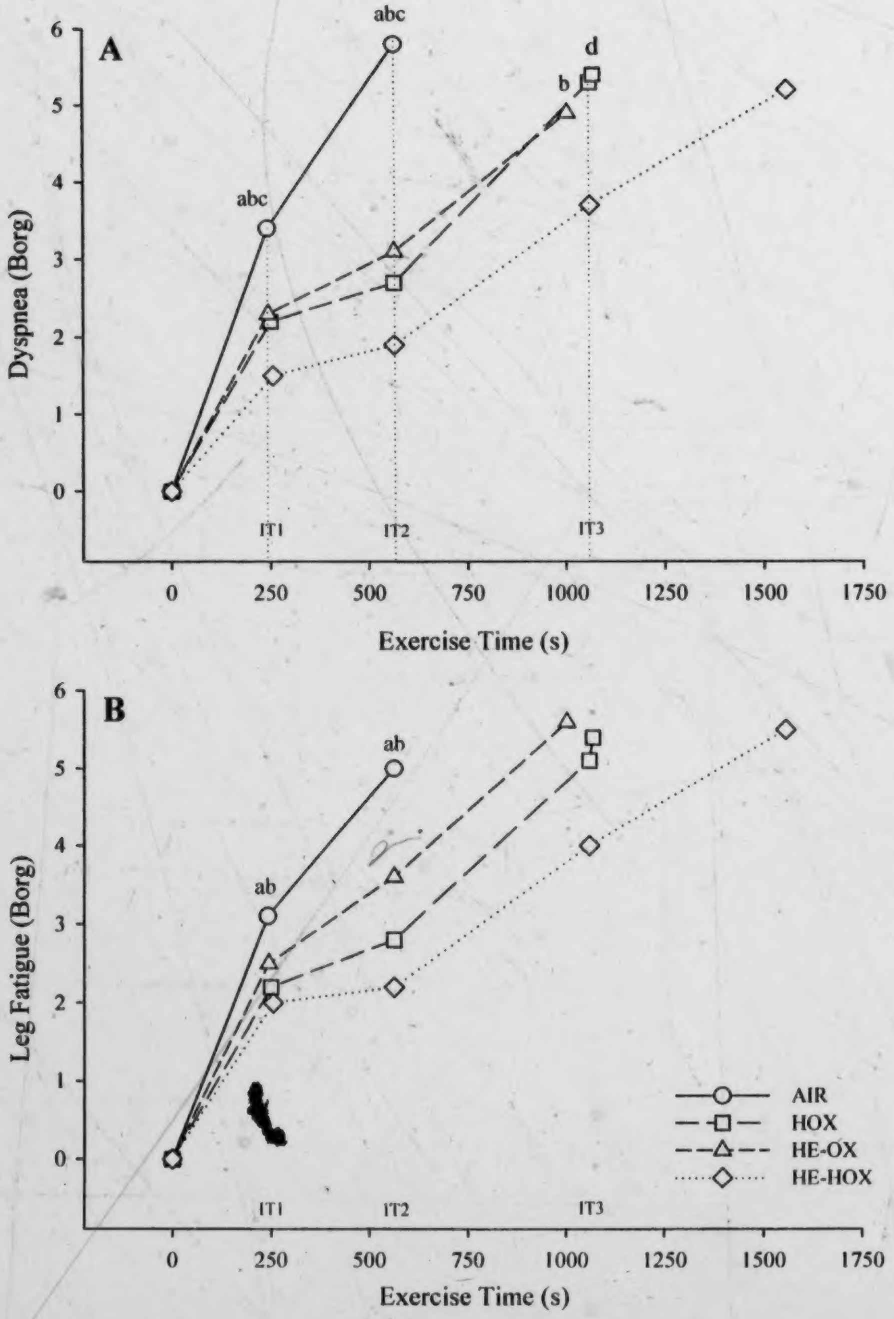

Figure V-3: The Borg ratings of exertional dyspnea (A) and leg fatigue (B) during the exercise tolerance tests while breathing HOX, HE-OX and HE-HOX. Comparisons are made at three iostimes (Please see text for explanation) and between peak values at end exercise a = AIR vs. HOX ($p < 0.05$); b = AIR vs. HE-OX ($p < 0.05$); c = AIR vs. HE-HOX ($p < 0.05$); d = HOX vs. HE-OX ($p < 0.05$).

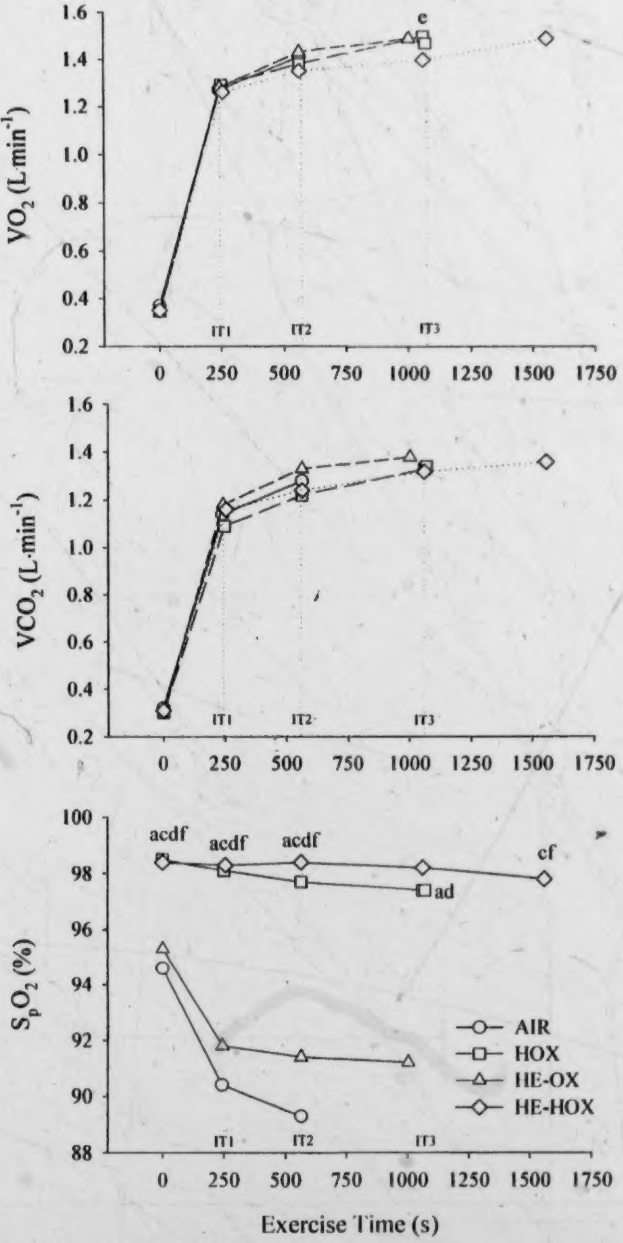

Figure V-4: The metabolic and oxyhemoglobin saturation responses to exercise. Top: oxygen consumption, Middle: carbon dioxide production and Bottom: oxyhemoglobin saturation (S_pO_2). Comparisons are made at three iostimes (Please see text for explanation) and between peak values at end exercise a = AIR vs. HOX ($p < 0.05$); c = AIR vs. HE-HOX ($p < 0.05$); d = HOX vs. HE-OX ($p < 0.05$); e = HOX vs. HE-HOX ($p < 0.05$); f = HE-OX vs. HE-HOX ($p < 0.05$).

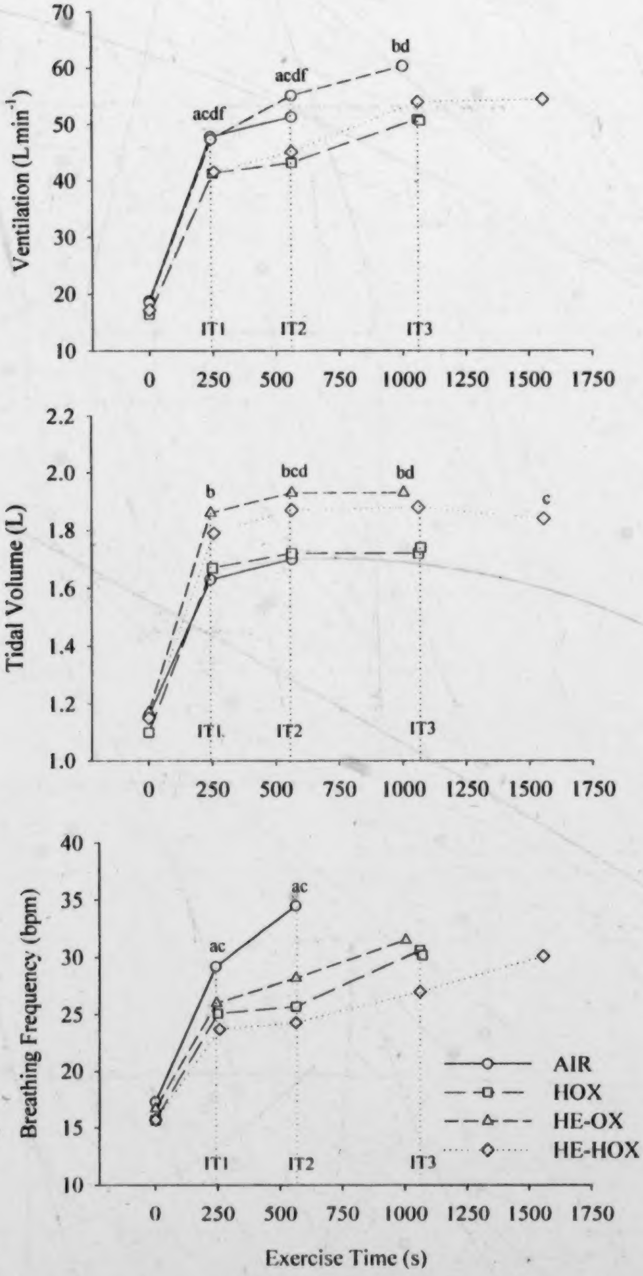

Figure V-5: The ventilatory responses to exercise. Top: ventilation, Middle: tidal volume and Bottom: breathing frequency. Comparisons are made at three iostimes (Please see text for explanation) and between peak values at end exercise a = AIR vs. HOX ($p < 0.05$); b = AIR vs. HE-OX ($p < 0.05$); c = AIR vs. HE-HOX ($p < 0.05$); d = HOX vs. HE-OX ($p < 0.05$); f = HE-OX vs. HE-HOX ($p<0.05$).

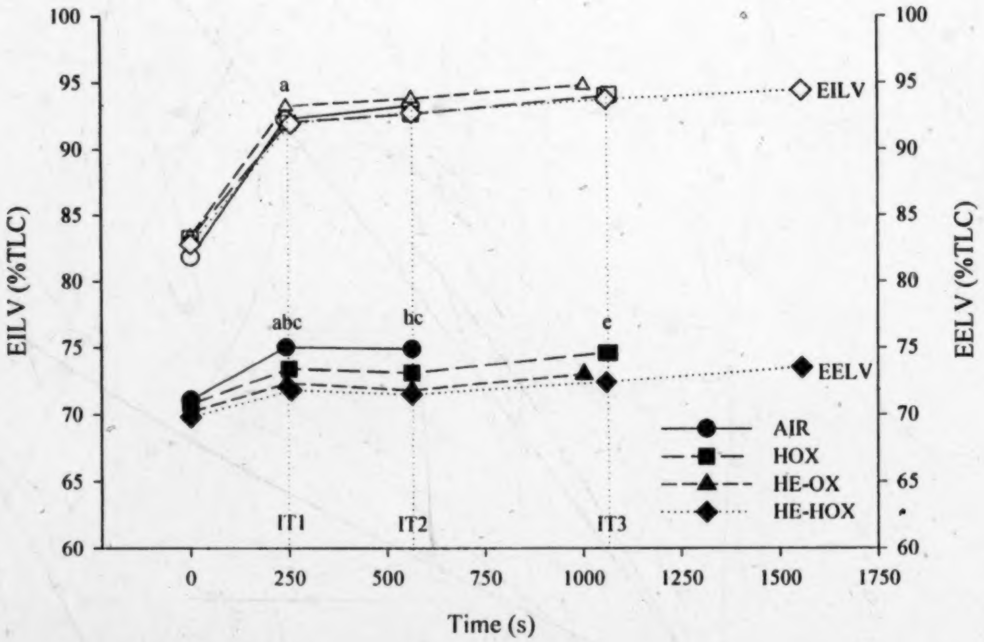

Figure V-6: Operational lung volumes measured during the exercise tolerance tests. EELV, end expiratory lung volume; EILV; end inspiratory lung volumes. Comparisons are made at three iostimes (Please see text for explanation) and between peak values at end exercise a = AIR vs. HOX ($p < 0.05$); b = AIR vs. HE-OX ($p < 0.05$); c = AIR vs. HE-HOX ($p < 0.05$); e = HOX vs. HE-HOX ($p < 0.05$).

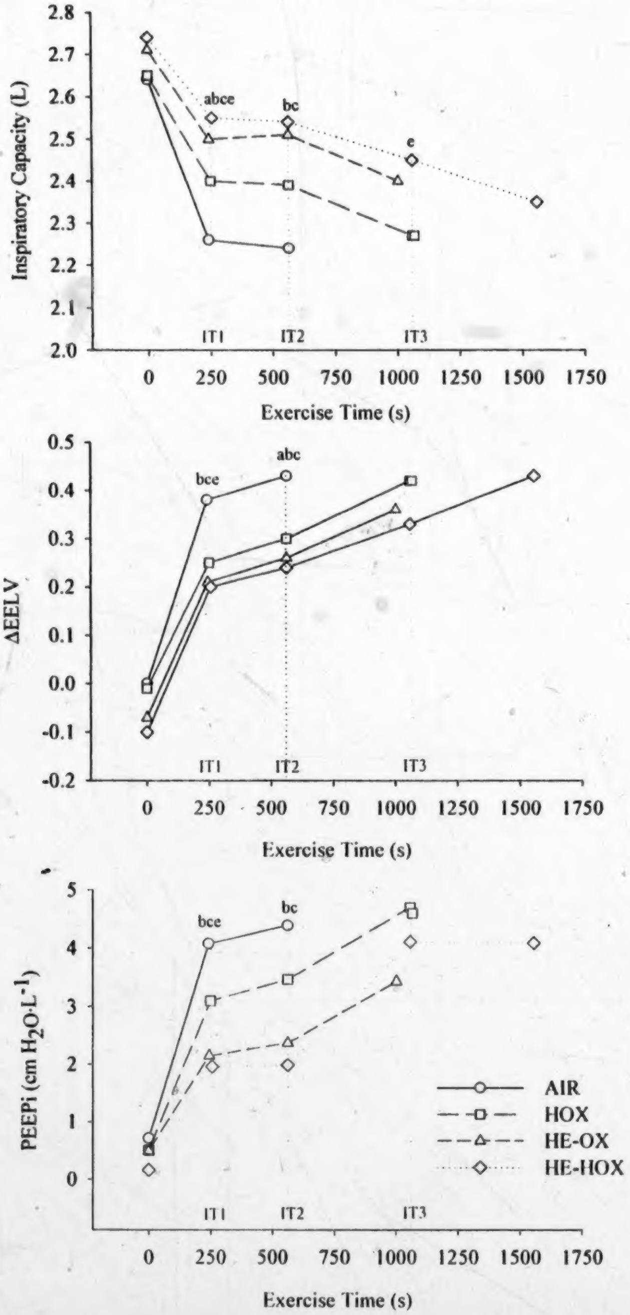

Figure V-7: Changes in inspiratory capacity (Top) EELV, end expiratory lung volume (Middle) and PEEPi, intrinsic positive end expiratory pressure (Bottom), during the exercise tolerance tests. Comparisons are made at three iostimes (Please see text for explanation) and between peak values at end exercise. a = AIR vs. HOX; b = AIR vs. HE-OX ($p < 0.05$); c = AIR vs. HE-HOX ($p < 0.05$); e = HOX vs. HE-HOX ($p < 0.05$).

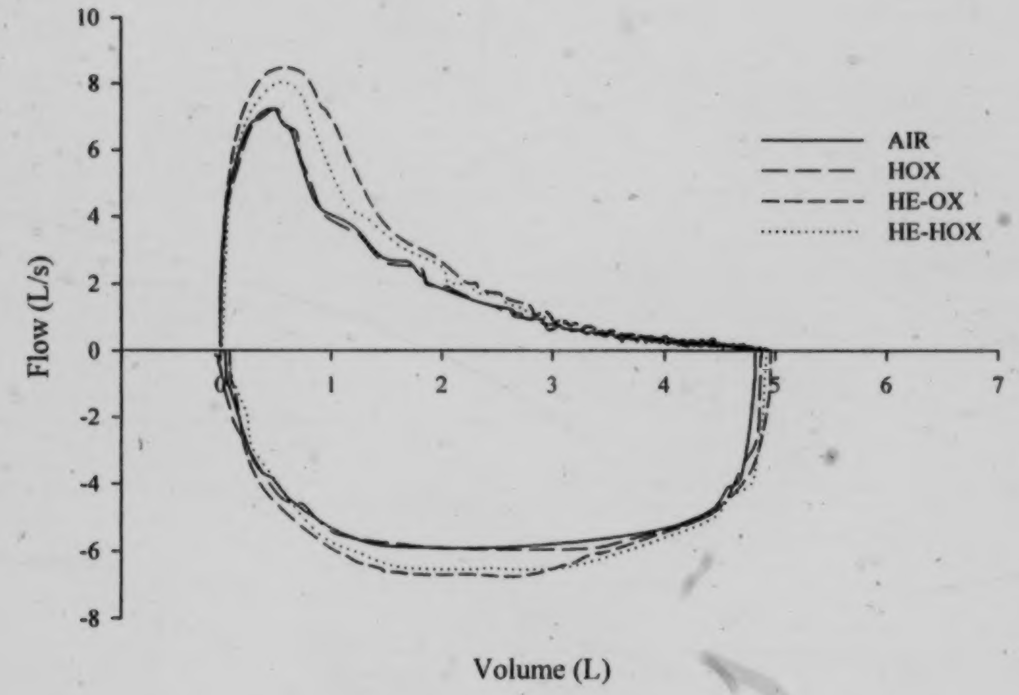

Figure V-8: Maximal flow-volume loops for one subject breathing the four gas mixtures.

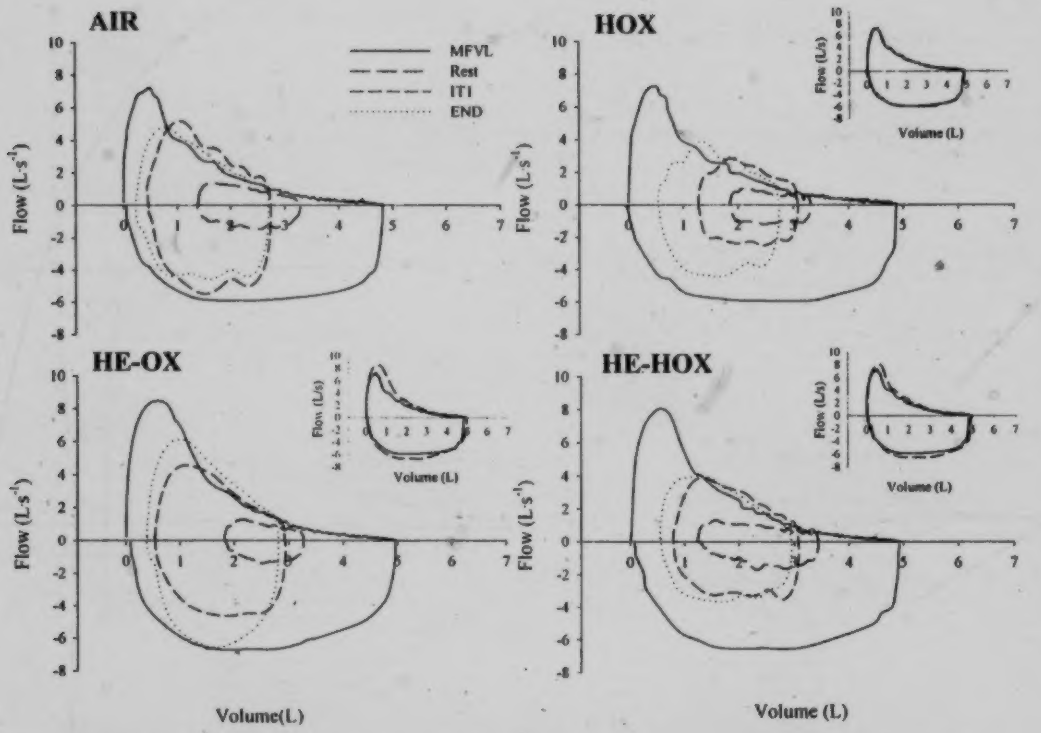

Figure V-9: Maximal and tidal flow-volume loops for one subject breathing the four gas mixtures. Maximal flow volume loops performed while breathing each gas mixture are depicted by the solid line (———). Tidal flow-volume loops measured at rest (— — —), the first (— —) isotime, and end exercise (··········) are also plotted. Insets: demonstrate the effect of each gas mixture on the maximal flow-volume loop compared to breathing air.

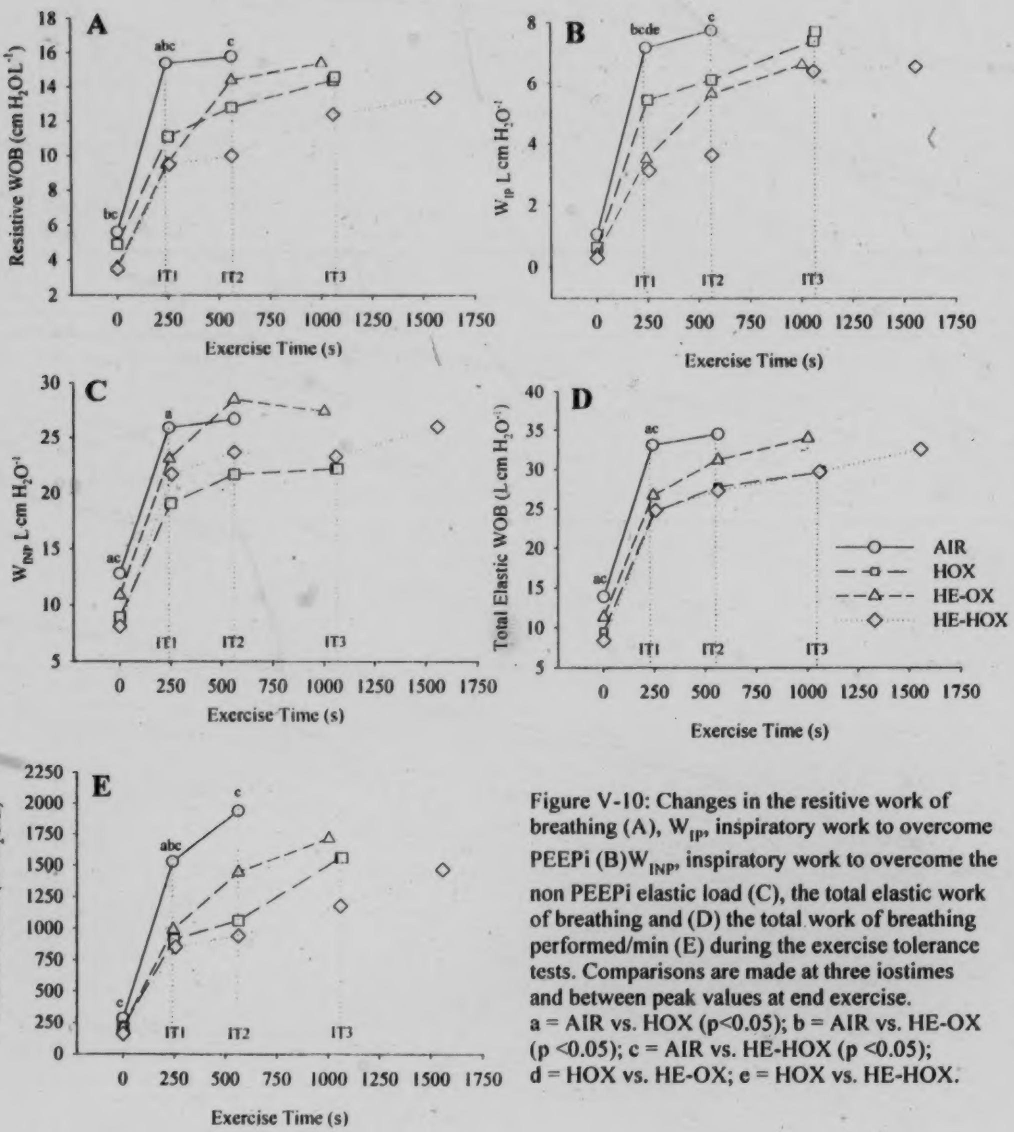

Figure V-10: Changes in the resitive work of breathing (A), W_{IP}, inspiratory work to overcome PEEPi (B)W_{INP}, inspiratory work to overcome the non PEEPi elastic load (C), the total elastic work of breathing and (D) the total work of breathing performed/min (E) during the exercise tolerance tests. Comparisons are made at three iostimes and between peak values at end exercise.
a = AIR vs. HOX ($p<0.05$); b = AIR vs. HE-OX ($p <0.05$); c = AIR vs. HE-HOX ($p <0.05$); d = HOX vs. HE-OX; e = HOX vs. HE-HOX.

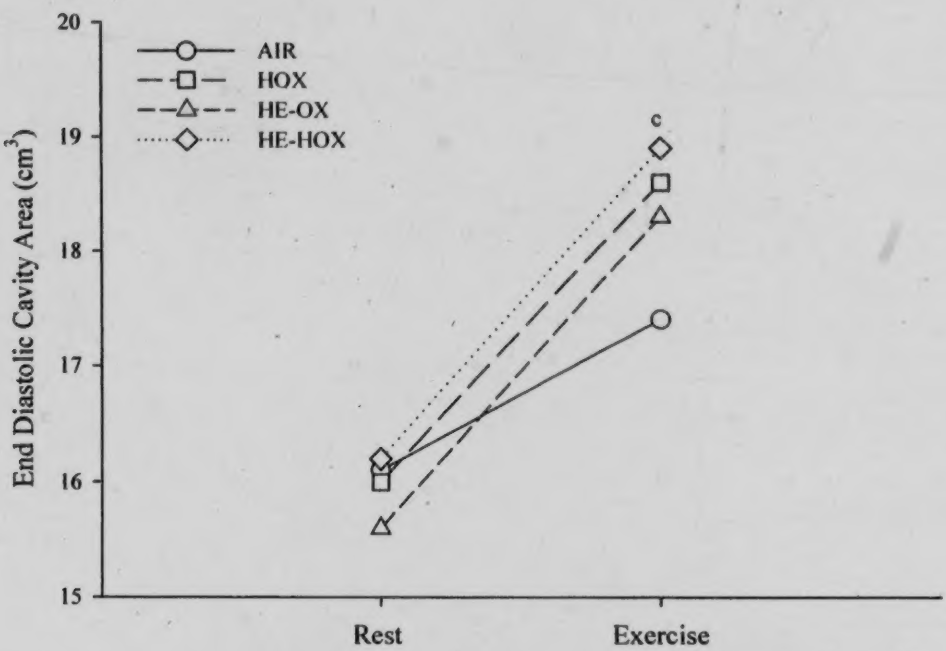

Figure V-11: The end diastolic cavity area response to breathing the different gas mixtures during rest and exercise. End diastolic cavity area signifcantly increased from resting values with HOX, HE-OX and HE-HOX but not air. c = AIR vs. HE-HOX ($p < 0.05$).

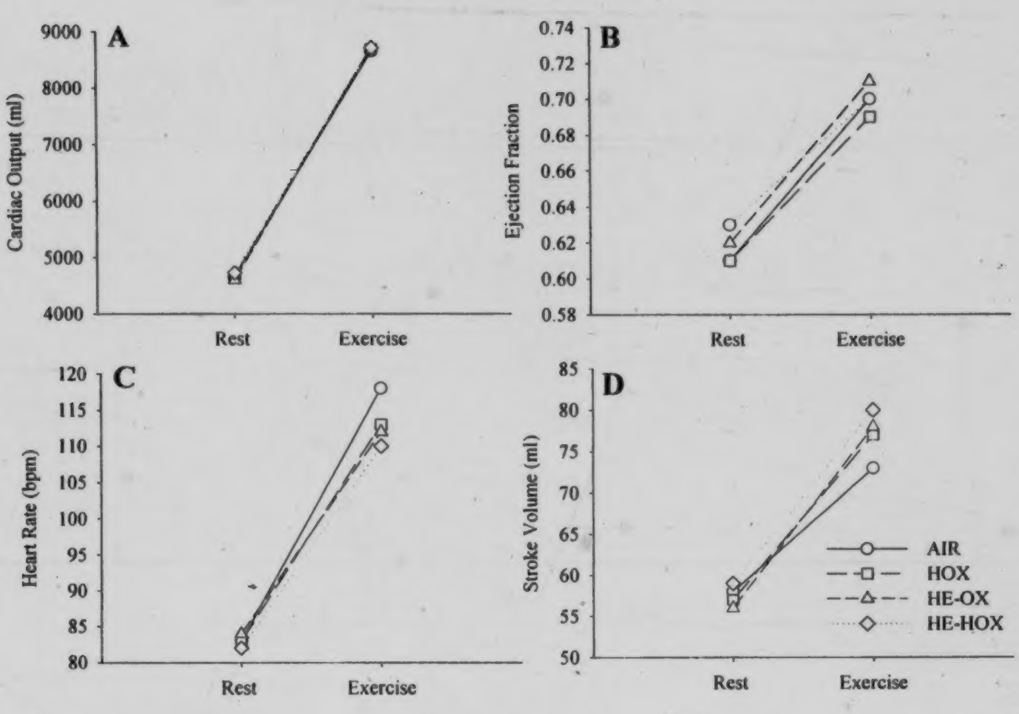

Figure V-12: The cardiovascular responses to exercise.

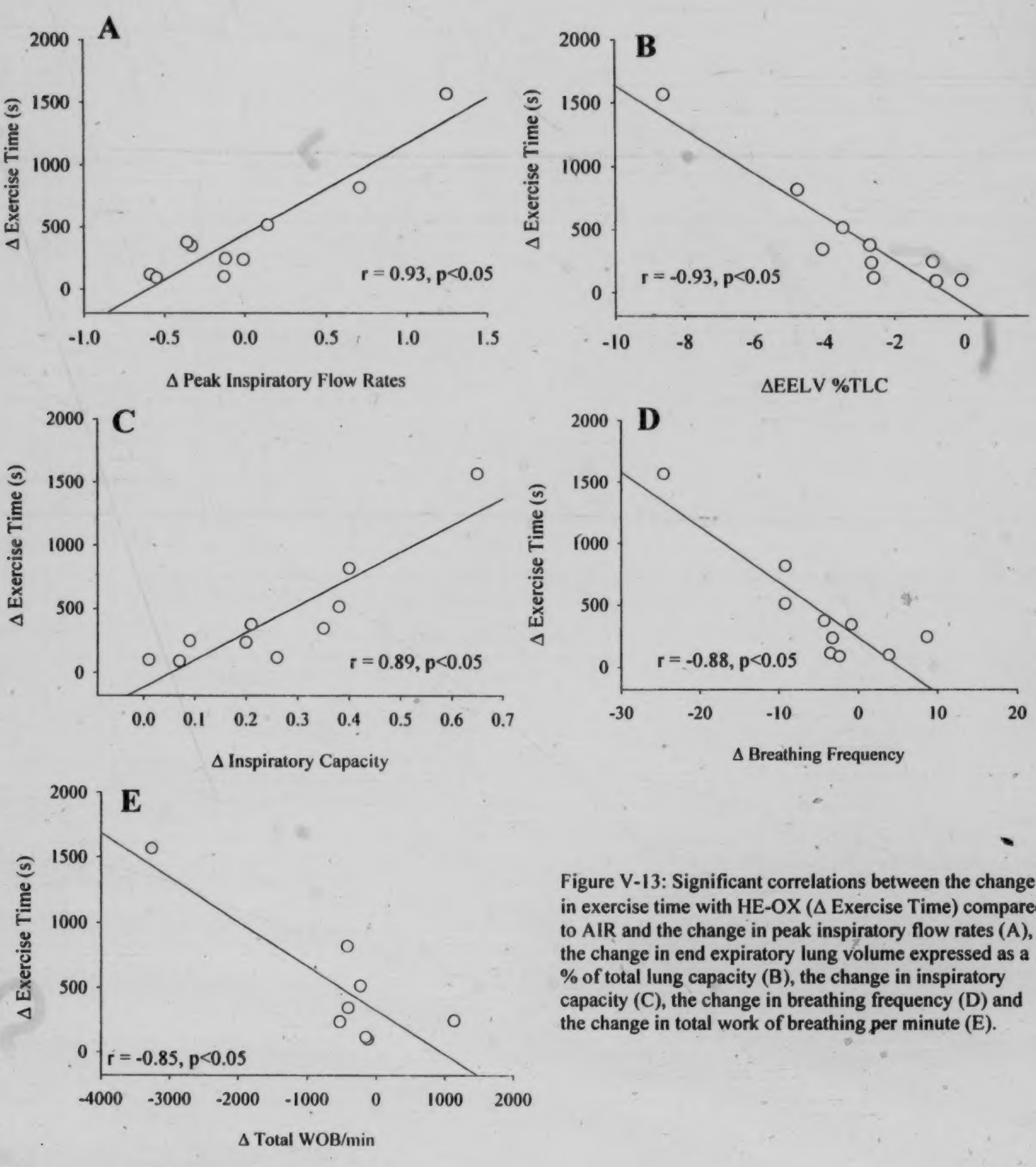

Figure V-13: Significant correlations between the change in exercise time with HE-OX (Δ Exercise Time) compared to AIR and the change in peak inspiratory flow rates (A), the change in end expiratory lung volume expressed as a % of total lung capacity (B), the change in inspiratory capacity (C), the change in breathing frequency (D) and the change in total work of breathing per minute (E).

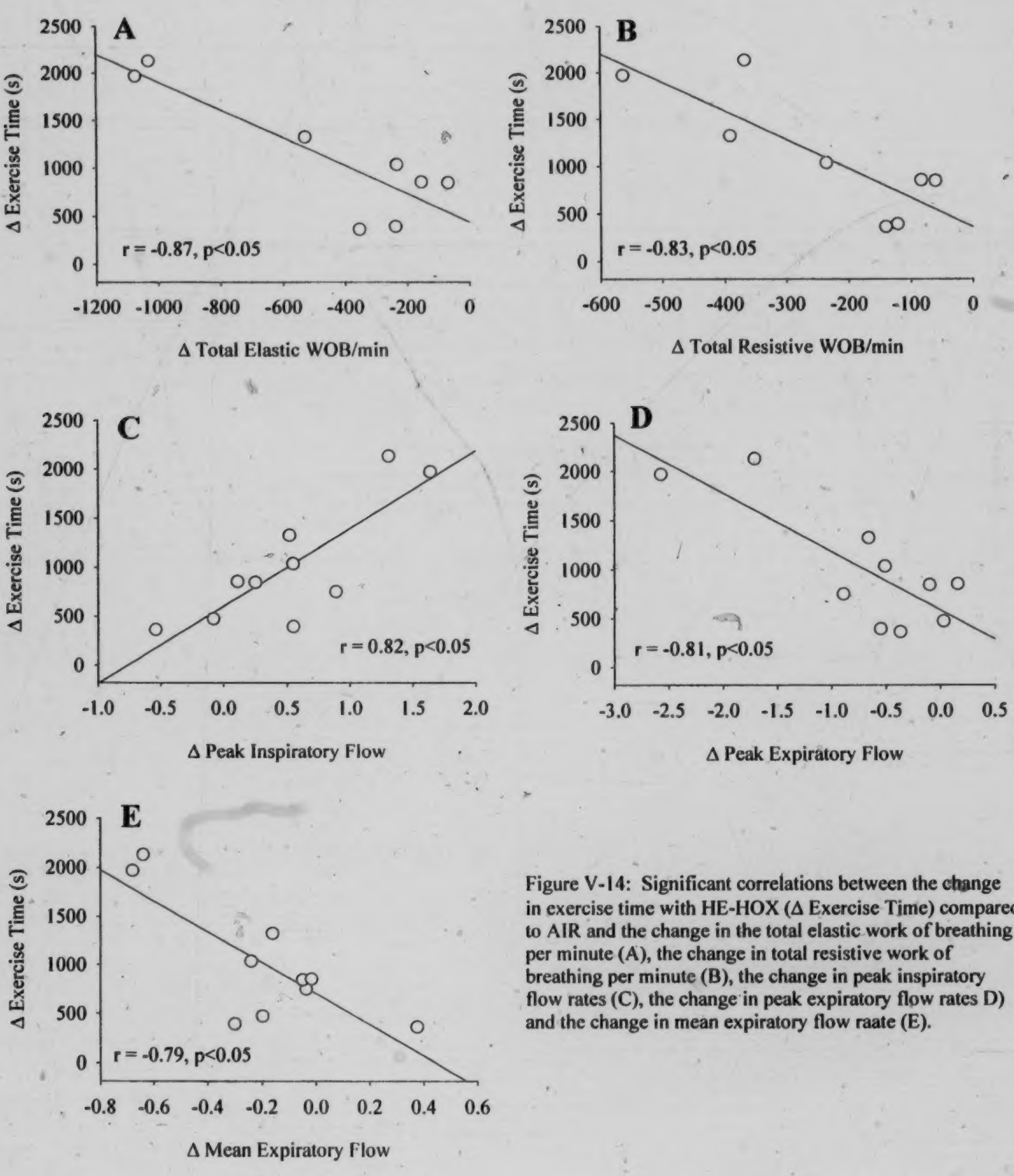

Figure V-14: Significant correlations between the change in exercise time with HE-HOX (Δ Exercise Time) compared to AIR and the change in the total elastic work of breathing per minute (A), the change in total resistive work of breathing per minute (B), the change in peak inspiratory flow rates (C), the change in peak expiratory flow rates D) and the change in mean expiratory flow raate (E).

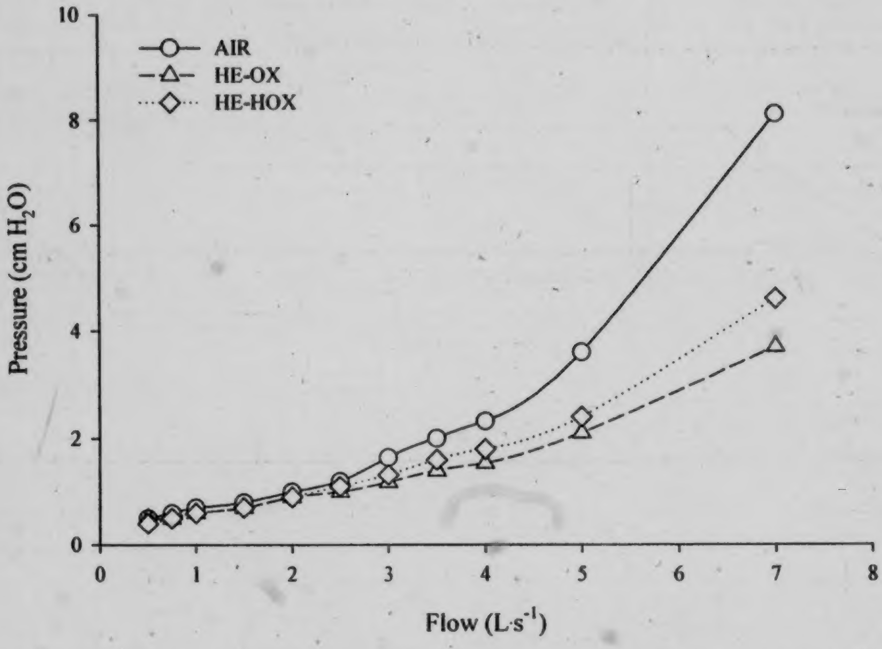

Figure V-15: Pressure-flow curves for the expiratory breathing circuit and spirometer.

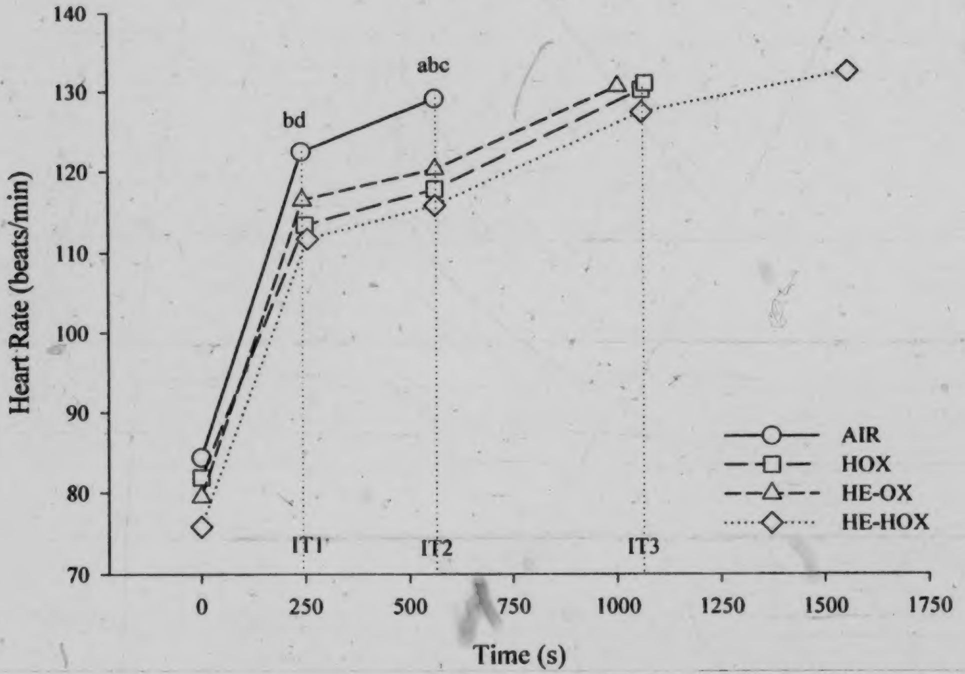

Figure V-16: The heart rate responses to exercise. Comparisons are made at three iostimes (Please see text for explanation) and between peak values at end exercise a = AIR vs. HOX ($p < 0.05$); b = AIR vs. HE-OX ($p < 0.05$); c = AIR vs. HE-HOX ($p < 0.05$).

CHAPTER VI

General Discussion

In the introductory chapter to this thesis, I hypothesized that the externally imposed expiratory resistance of the self-contained breathing apparatus (SCBA) attenuates ventilation (V_E) and reduces exercise capacity. Furthermore, evidence was presented demonstrating how the expiratory flow limitation associated with the high internal airway resistance and reduced lung elastic recoil of COPD patients constrains V_E and limits exercise tolerance. As a result, I proposed that normoxic and hyperoxic helium-based gas mixtures could reduce these ventilatory limitations and improve exercise tolerance in both circumstances. The three studies that were performed to test these theories are presented in the preceding chapters.

The first study was designed to quantify the effects of the SCBA on ventilation (V_E) and maximal oxygen consumption (VO_{2max}) in healthy individuals. A secondary aim of this preliminary study was to determine whether the externally imposed breathing resistance of the SCBA regulator or the thoracic restriction imposed by the straps, harness and weight of the SCBA cylinder assembly, were responsible for any of the reductions in V_E or VO_{2max} observed. The findings from this initial investigation demonstrated that the modern SCBA often used by firefighters reduces maximal V_E, which results in a reduction in VO_{2max} of 14.9 ± 7.1%. The main cause of this limitation was the externally imposed breathing resistance of the SCBA regulator, as the reductions in V_E and VO_{2max} when only the regulator was worn were comparable to those observed with the full SCBA. However, the thoracic restriction imposed by the weight of the SCBA air cylinder and the shoulder and waist straps of the SCBA harness were also found to contribute to the reduced exercise capacity as a significant 4.8 ± 5.3% reduction in VO_{2max} was also observed with this piece of equipment.

While the added expiratory resistance of the SCBA had a sizeable effect on VO_{2max}, expiratory flow rates were not greatly affected by the SCBA at submaximal levels. However, in order to prevent expiratory flow limitation from occurring, much greater expiratory pressures had to be generated. This compensatory mechanism used to overcome expiratory resistance was effective in most individuals up to a ventilation of 110 $L \cdot min^{-1}$. However, above this V_E, a reduced expiratory flow rate was observed despite the elevated expiratory effort. These findings have a number of implications for individuals who perform physical work with the SCBA. Firstly, while the SCBA does not appear to affect ventilatory function at low to moderate intensities, it may reduce exercise capacity during bouts of high or maximal intensity work. Secondly, as a greater expiratory pressure is needed to maintain adequate expiratory flow rates at a submaximal level, it is possible that prolonged work on the SCBA may lead to respiratory muscle fatigue.

Considering these limitations identified in the first study, interventions that would alleviate breathing resistance were explored. As helium has a lower density than nitrogen, with only a slightly increased viscosity, it maintains laminar flow for longer and markedly reduces airway resistance (Brice and Welch, 1983; Babb, 2001). It was believed that these physical attributes of helium could reduce the turbulent flow in the SCBA regulator, and increase maximal V_E. Furthermore, as previous work by the author had identified that hyperoxia could improve VO_{2max} when wearing the SCBA (Eves et al., 2002a), we were also interested in the potentially greater benefit that combining the two gas mixtures could have on maximal and submaximal exercise performance. Therefore, a second study was designed to investigate the possible benefits of breathing a helium-based gas to reduce these limitations. The findings of this study were separated into two manuscripts with the results reported in Chapters III and IV.

The responses to maximal exercise seen while breathing normoxic-helium (HE-OX) and hyperoxic-helium (HE-HOX) from the SCBA, are presented in Chapter III. The original finding from this study demonstrated that both HE-OX and HOX improved VO_{2max} by 10.2 ± 6.3% and 12.9 ± 5.6%, respectively. However, HE-HOX improved VO_{2max} by 21.8 ± 5.6%. With both helium-based gas mixtures, the improvements in VO_{2max} were associated with an increase in V_E of approximately 25% and a markedly reduced expiratory breathing resistance. These findings demonstrate that the HE-OX mixture reverse the mechanical constraint imposed by the SCBA on maximal exercise performance. Furthermore, the greater improvement in VO_{2max} observed with HE-HOX suggests that this gas mixture can combine the benefits of the lower density helium for improving V_E with the elevated oxyhemoglobin saturation associated with HOX. However, as hyperoxia alone appears to nullify the oxyhemoglobin desaturation observed with the SCBA, the benefits of the helium gas appear to transcend improvements in arterial saturation.

It is possible that this beneficial effect of helium may be due to an unloading of the respiratory muscles during heavy exercise. Harms et al., (1997, 1998) demonstrated that respiratory unloading with a proportional assist ventilator decreased the O_2 demand of the respiratory muscles and enhanced O_2 delivery by a redistribution of blood flow to the exercising muscles. The reduced peak inspiratory and expiratory mouth pressures found at maximal exercise suggest that the work of breathing was reduced. However, as tidal volume was increased at maximal exercise with the helium gases, the elastic component of the work of breathing may actually be increased. Therefore, although this is an attractive postulate to explain the difference in VO_{2max} with the HE-OX and HE-HOX gases, further research is needed to address whether there actually is a beneficial effect of helium on the work of breathing when using the SCBA.

A secondary aim of this study was to address the possible benefits of helium-oxygen gas mixtures during submaximal exercise. More specifically, a subsidiary project investigated whether HE-OX and HE-HOX could also reduce the breathing resistance and expiratory pressures needed to maintain relatively high submaximal ventilations. The major findings of this investigation are reported in Chapter IV. It was established that similar to maximal exercise, the external expiratory breathing resistance of the SCBA and the expiratory mouth pressures needed to maintain expiratory flow rates were significantly reduced with the helium gases. Additionally, at end exercise V_E was not increased with either HE-OX or HE-HOX and reached approximately 85-95 $L \cdot min^{-1}$. This result supports the findings of the first study that demonstrated that with compressed air, expiratory flow rates were adequate to maintain V_E below 110 $L \cdot min^{-1}$ with the SCBA. Moreover, it also suggests that when breathing from the SCBA helium only increases V_E when an expiratory flow limitation is present.

Despite the fact that the occurrence of respiratory muscle fatigue has not been studied with the SCBA, the significant reduction in maximal inspiratory and expiratory pressures found following the compressed air trial supplies preliminary evidence to suggest that this may occur. Moreover, the ability to maintain maximal respiratory pressures with the helium mixtures demonstrates that the reduced pressure generation needed to breathe with helium is beneficial for avoiding fatigue. Whether these findings actually indicate the presence of respiratory muscle fatigue with the SCBA cannot be clarified by the findings of the second study. However, if this phenomenon does occur, it could reduce respiratory muscle performace and exercise tolerance during sustained or repeated bouts of work.

Few additional benefits of breathing a helium-hyperoxic gas mixture over HOX or HE-OX during submaximal exercise were observed, however, the participants did report a significantly lower perceived exertion at the end of the HE-HOX trial. As the duration of each test was kept constant, it remains unknown whether this finding would translate into a greater exercise tolerance with the HE-HOX gas. Nevertheless, the reduced breathing resistance and the lower blood lactate levels observed during exercise with HE-HOX suggest that this is not an unrealistic suggestion.

The collective findings of the second study demonstrated that helium-based gas mixtures reduced the external breathing resistance of the SCBA at both submaximal and maximal intensities. Furthermore, when expiratory flow was impeded during moderate to heavy work with the SCBA, the helium induced resistive unloading increased V_E, enhanced tidal volume and improved VO_{2max}. The most noteworthy outcome of the second study was the superior effect of helium-hyperoxia for improving exercise capacity over either normoxic-helium or a nitrogen-based hyperoxic gas. A natural progression was to investigate the possible benefits of helium hyperoxia for improving the exercise tolerance of individuals who have a pathophysiological expiratory flow limitation and markedly increased internal airway resistance, as seen in patients with COPD.

As discussed in Chapters I and V, many studies have previously demonstrated how COPD patients dynamically hyperinflate during exercise due to expiratory flow limitation (Diaz et al., 2000; Marin et al., 2001, O'Donnell et al., 2001). This abnormal increase in lung volume has been shown to heighten exertion dyspnea, which attenuates exercise tolerance (O'Donnell et al., 2002). Therefore, the final study was designed to investigate the potential benefits of helium-hyperoxia for improving the exercise tolerance of COPD patients. Furthermore, to investigate how improvements in pulmonary and cardiovascular function are related to any improvements observed in exercise tolerance; operational lung volumes, the work of breathing and cardiovascular function were measured during exercise.

The primary finding of the final investigation was similar to the findings obtained from the SCBA study, in that helium-hyperoxia had a significantly greater effect on the exercise tolerance of COPD patients than either HOX or HE-OX. During a constant load trial to symptom limitation, HE-HOX increased the amount of exercise performed by patients with moderate to severe COPD by 245 ± 208%, 54 ± 41% and 92 ± 30% compared to air, HOX and HE-OX, respectively. Significant reductions in the symptoms of dyspnea and leg fatigue were also observed. These results, specifically the marked increase in exercise tolerance coupled with a reduced dyspnea and leg fatigue have significant implications for improving the functional status of COPD patients.

The mechanisms responsible for enhanced exercise tolerance with HE-HOX are related to the improved lung volumes and reduced work of breathing. Using repetitive inspiratory capacity (IC) maneuvers, a significant reduction in dynamic hyperinflation with all three experimental gas mixtures was found compared to air. However, as exercise time increased, the benefits of helium-hyperoxia for maintaining end expiratory lung volume (EELV) surpassed the other two interventions. Maintaining EELV at a lower percentage of TLC increases tidal volume, without a concomitant increase in the work of breathing. This more efficient breathing pattern appears to be primarily responsible for the improved dyspnea with HE-HOX, as a significant relationship between the reductions in ventilatory constraint (V_T/IC) and breathing discomfort was found. The reduced EELV seen with HE-HOX can be explained by the reduced ventilatory demand with this gas. More specifically, the attenuated V_E reduces expiratory flow limitation thorough a decrease in expiratory flow rate, while the reduced breathing frequency prolongs expiratory time and allows a greater volume of air to be expelled from the lungs. Therefore, as exercise duration increases, the enhanced expiratory time with HE-HOX appears to be the key factor for maintaining EELV at a lower percentage of TLC and thus enhancing tidal volume.

At symptom limitation with HE-OX, maximal V_E was increased. This demonstrates the ability of normoxic-helium to reduce expiratory flow limitation in individuals with COPD. HE-OX also improved tidal volume but unlike HE-HOX this was achieved by increasing both inspiratory and expiratory flow rates rather than reducing ventilatory demand. HE-HOX did not significantly improve maximal V_E in COPD patients even though the maximal flow-volume envelope was enhanced. As exercise was terminated in the HE-HOX trial primarily due to leg fatigue, it remains unknown whether ventilation can be increased to a similar level to that observed with HE-OX.

Helium-hyperoxia also possessed additional qualities for reducing the work of breathing. While all three experimental gas mixtures decreased the resistive work of breathing during the early stages of exercise, only HE-HOX maintained a lower resistive work at a time comparable to end exercise in the air trial. The greater reductions in the resistive work of breathing observed with HE-HOX can be explained by the reduced flow rates associated with hyperoxia in concert with the reduced airway resistance of helium. The combination of helium and hyperoxia also produced greater reductions in the elastic work of breathing. Compared to HOX, a greater reduction in the elastic work to overcome PEEPi was observed. While compared to HE-OX, HE-HOX reduced the work performed to overcome the elastic recoil of the lung. These findings of an enhanced tidal volume with HE-HOX in combination with a reduced work of breathing clearly demonstrate that HE-HOX maintains a more efficient breathing pattern during exercise compared to the other gas mixtures. A number of previous studies have demonstrated that the increased inspiratory pressure generation associated with dynamic hyperinflation is the primary contributor to dyspnea and exercise intolerance in COPD (Killian and Jones, 1981; Iandelli et al., 2002). Therefore, it is not surprising that the reductions observed in the elastic work of breathing with HE-HOX were associated with the vast improvements in exercise tolerance.

Previous studies have demonstrated an adverse cardiovascular response to exercise in COPD (Slutsky et al., 1981; Stewart and Lewis, 1986; Oelberg et al., 1998), which has led to a number of hypotheses regarding the effects of dynamic hyperinflation on cardiovascular function (Whittenberger et al., 1968, Potter et al., 1971; Butler et al. 1988). As discussed in detail in Chapters I and V it is feasible that the increased lung volumes observed during exercise reduce LV filling through abnormal right ventricular mechanics. Support for this hypothesis is provided by the data from this third study, as end diastolic cavity area was improved with HE-HOX, and the reduced PEEPi and dynamic hyperinflation combined to explain 81% of the variance in LV end diastolic cavity area. Although these findings provide preliminary evidence of a relationship between the abnormal pulmonary mechanics in COPD and the associated irregular cardiovascular responses to exercise, more work is needed to understand the precise mechanisms responsible for the improved left ventricular filling.

Summary

In summary, the most unique finding of the three studies conducted, was that helium-hyperoxia combined the benefits of both normoxic-helium and hyperoxia to have a superior effect on the exercise capacity of COPD patients and individuals wearing the SCBA. More specifically, helium-hyperoxia reduced the external expiratory breathing resistance imposed by the SCBA regulator, decreased peak expiratory pressure, improved ventilation and concomitantly improved oxyhemoglobin saturation. Together, these combined findings resulted in reduced perceptions of exertion during submaximal exercise and vastly improved maximal oxygen consumption.

In individuals with moderate to severe COPD, helium-hyperoxia improved operational lung volumes and decreased the work of breathing. These findings were associated with reduced exertional dyspnea and greatly enhanced exercise tolerance. Additionally, HE-HOX also improved LV end diastolic cavity area through a reduction in dynamic hyperinflation. Collectively, the findings of the three studies performed demonstrate the potential benefits of helium hyperoxia for improving maximal exercise capacity with the SCBA and the cardiopulmonary response to exercise in COPD patients. Thus, this data provides fundamental knowledge for furthering the understanding of the significant benefits this unique gas mixture has for improving both occupational performance and exercise tolerance in a clinical population.

Future Studies

The findings from the three studies performed in this thesis raise a number of questions that should be addressed in future research projects. Firstly, although the effect of the different components of the modern SCOTT SCBA are now fairly well understood, it is still unclear whether this particular SCBA actually increases the work of breathing. It is demonstrated in Chapter II that expiratory mouth pressure is increased with the SCBA, which suggests expiratory muscle work is increased. However, the tendency to breathe with a reduced tidal volume when wearing the SCBA would result in a reduction in the elastic work of breathing as long as operational lung volume are similar to that observed with mouth breathing. Therefore, the next study should investigate the effect of the SCBA on operational lung volumes and the work of breathing at ventilation rates above and below 110 $L \cdot min^{-1}$.

To accurately measure the work of breathing with the SCBA raises a number of technical issues that need to be addressed before this study can be performed. Although, it is now relatively simple to measure expired volume with the SCBA, a problem arises when trying to measure inspired gas volume. With the SCOTT SCBA used by our lab, the inspiratory gas mixture is passed directly from the air cylinder to the wearer via a number of pressure regulators. As a result, inspiratory volume cannot be measured using a pneumotach or spirometer. In fact, the only technique that will allow accurate spontaneous pressure-volume measurements to be performed with the SCBA is to exercise in a large body plethysmograph. This type of measurement has previously been employed in a number of exercise studies (Stubbing et al., 1980). However, it still remains to be investigated whether accurate inspiratory volumes can be obtained when exercise performed with the SCBA.

A number of questions still need to be answered about the use of helium gas mixtures with the SCBA. Firstly, whether helium oxygen gas mixtures actual reduce the work of breathing with the SCBA has yet to be documented. Preliminary evidence from the studies reported in Chapters III and IV suggest that both inspiratory and expiratory work of breathing is reduced at submaximal ventilation rates. However, this may not be the case at maximal exercise where tidal volume and minute ventilation were greatly enhanced with both HE-OX and HE-HOX. Secondly, further studies are needed to evaluate whether the respiratory muscles actually fatigue when repetitive bouts of exercise with the SCBA are performed. This question is an important one as firefighters often perform two bouts of work when fighting a fire and a decrease in respiratory muscle performance would have a number of implications for performance and safety. Furthermore, if respiratory muscle function is reduced, then helium-based gas mixtures maybe useful in preventing such an occurrence. To accurately answer this question, however, a more accurate effort independent measurement of respiratory muscle fatigue such as phrenic nerve stimulation would be needed.

The greater improvements in exercise tolerance with HE-HOX in a COPD population compared to breathing air or a nitrogen based hyperoxic gas mixture raises a number of interesting questions. However, the natural progression from this initial study would be to perform a randomized control trial to investigate whether helium-hyperoxia can enhance the benefits of the exercise-training component of a pulmonary rehabilitation program. It is now well accepted that a multidisciplinary pulmonary rehabilitation program that incorporates exercise training is an effective technique for increasing exercise tolerance (O'Donnell et al., 1997; Bernard et al., 1999; Casaburi et al., 1997; Lacasse et al., 1996) improving the ability to perform activities of daily living (Bendstrup et al., 1997) and for enhancing health-related quality of life (Gosselink et al., 1997; Goldstein et al., 1994). Furthermore, Griffiths et al., (2000), demonstrated that completion of an outpatient pulmonary rehabilitation program improved the health status of COPD patients, which significantly decreased the use of health services and reduced the financial burden on the health care system (Griffiths et al., 2001). It therefore stands to reason that any intervention that can improve the volume of exercise that can be completed during a pulmonary rehabilitation program would also have additional effects on exercise tolerance and quality of life in this population.

A recent study by Emtner et al., (2003) demonstrated that oxygen supplementation delivered while performing exercise training allowed COPD patients to train at higher exercise intensities and resulted in greater gains in exercise tolerance. However, as reported in Chapter V hyperoxia does not improve expiratory flow rates, minute ventilation, dynamic hyperinflation or dyspnea compared to room air. These findings suggest that although a higher work capacity may be possible with hyperoxia, exercise limitation and dyspnea will still limit the exercise intensity that patients can exercise at and may not allow optimal improvements in exercise capacity.

In contrast, the findings from the final study of this thesis (Chapter V) demonstrated that helium-hyperoxia produced greater reductions in dynamic hyperinflation, work of breathing and dyspnea than either normoxic-helium or a nitrogen-based hyperoxia gas. Furthermore, it was also found that with helium-hyperoxia seven out of ten patients stopped exercising due to leg fatigue while only two stopped due to dyspnea. This is significantly different from the room air trials where seven stopped due to dyspnea and two stopped from leg fatigue. This finding provides some evidence that a helium-hyperoxic gas mixture can alleviate dyspnea to an extent that skeletal muscle function becomes more of a limiting factor to exercise tolerance than shortness of breath. More importantly perhaps, helium-hyperoxia may now allow patients to exercise at intensities that will specifically target improvements in skeletal muscle function. If true, this hypothesis could have considerable implications for individuals with COPD. Previously research has demonstrated that exercise training cannot improve lung function in COPD patients (Emtner et al., 2003). However, improvements in skeletal muscle morphology and metabolism may be crucial for increasing functional capacity (Serres et al., 1997; Maltais et al., 1996) and for reducing some of the systemic effects of the disease (Wouters et al., 2002).

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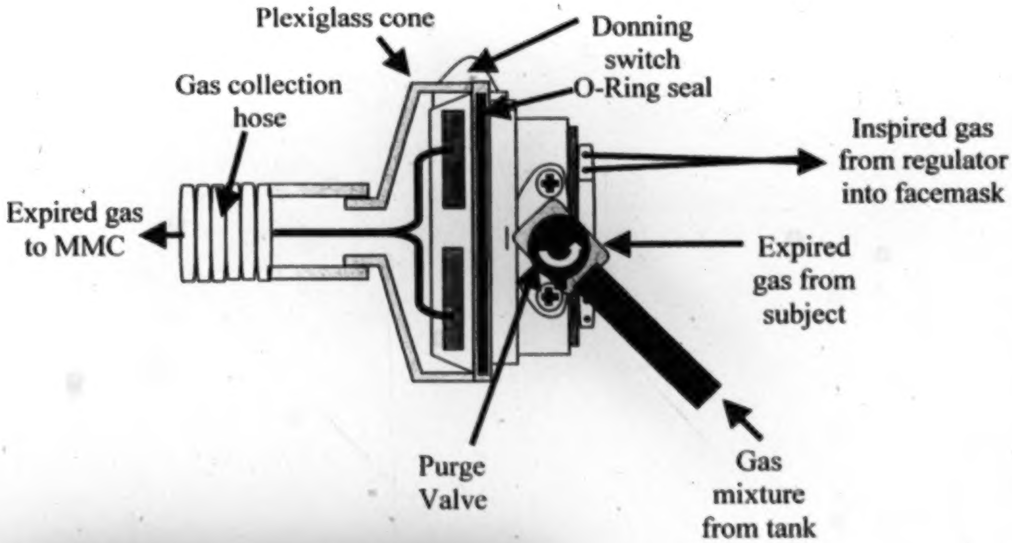
APPENDIX A

EXPERIMENTAL APPARATUS


Plexiglass cone
Donning switch
O-Ring seal
Gas collection hose
Inspired gas from regulator into facemask
Expired gas to MMC
Expired gas from subject
Purge Valve
Gas mixture from tank

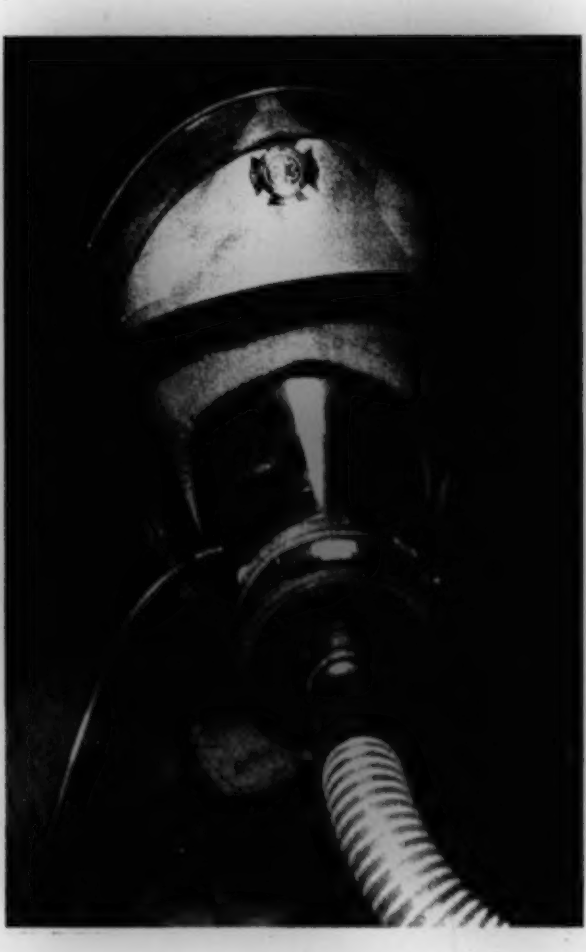


Figure A-1: (Above) Schematic of the plexiglass cone that was designed to collect the expired gases from the SCBA regulator

Figure A-2: (Left) Plexiglass cone attached to the SCBA regulator. The tube on the left of the picture measured mask pressure.

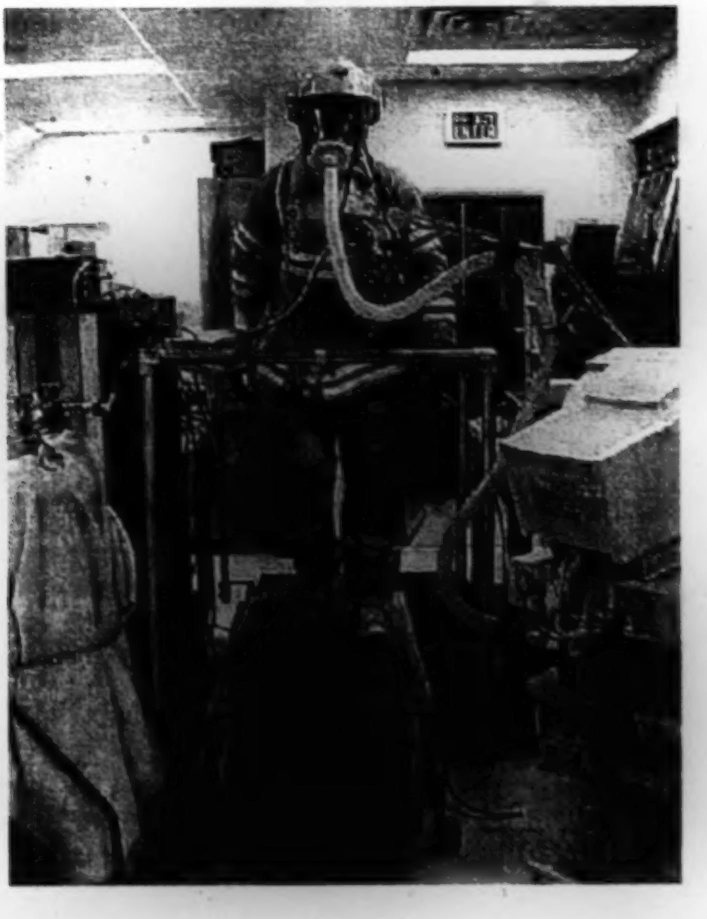


Figure A-3: Experimental set-up for the second study. Subjects wore full protective clothing and expired gases were collected and measure by the metabolic cart on the right of the picture. The gas tanks containing the experimental gas mixtures are covered and stand to the left of the treadmill.

Figure A-4: Exercise echocardiographic assessment of left ventricular function.

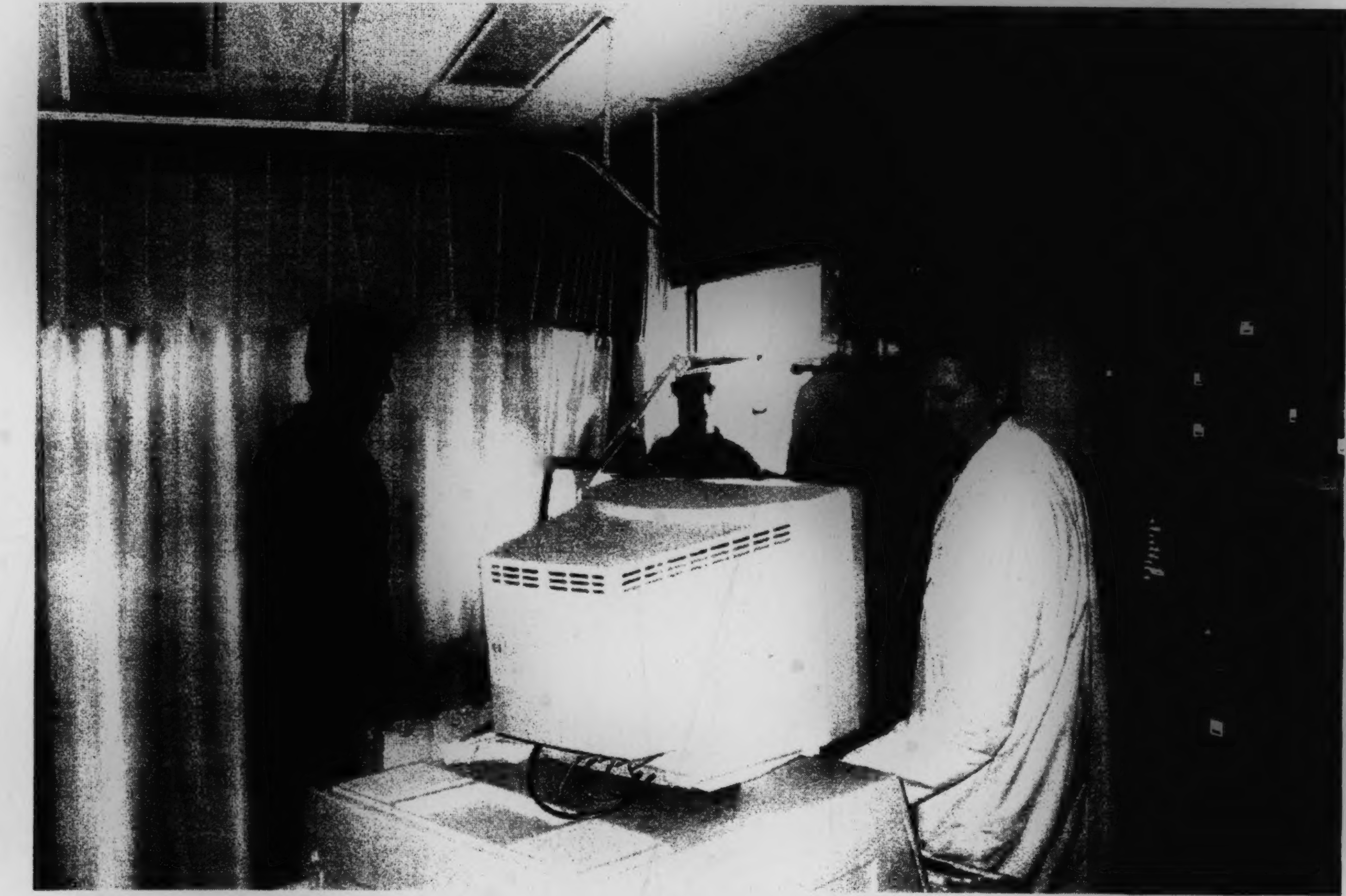


Figure A-5: Exercise echocardiographic assessment of left ventricular function. Gas tanks delivering the gas mixtures are hidden behind the curtain to keep the subject blind to the gas mixture used.

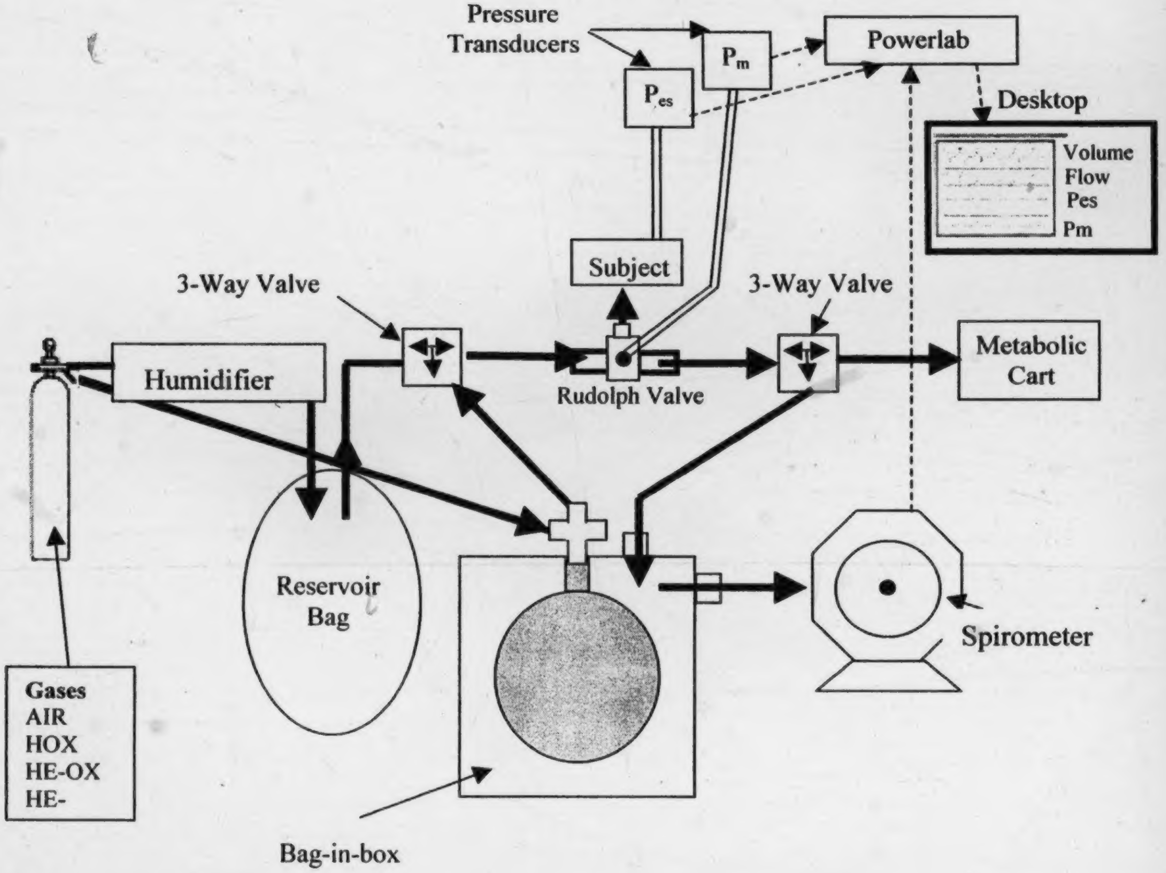

Pressure
Transducers
P_m
Powerlab
P_{es}
Desktop
Volume
Flow
Pes
Pm
Subject
3-Way Valve
3-Way Valve
Humidifier
Rudolph Valve
Metabolic
Cart
Reservoir
Bag
Spirometer
Gases
AIR
HOX
HE-OX
HE-
Bag-in-box

Figure A-6: schematic of the breathing circuit used during the exercise tolerance trials. Thick black arrows designate path of airflow. Thin dashed lines indicate outputs from pressure transducers and the spirometer.

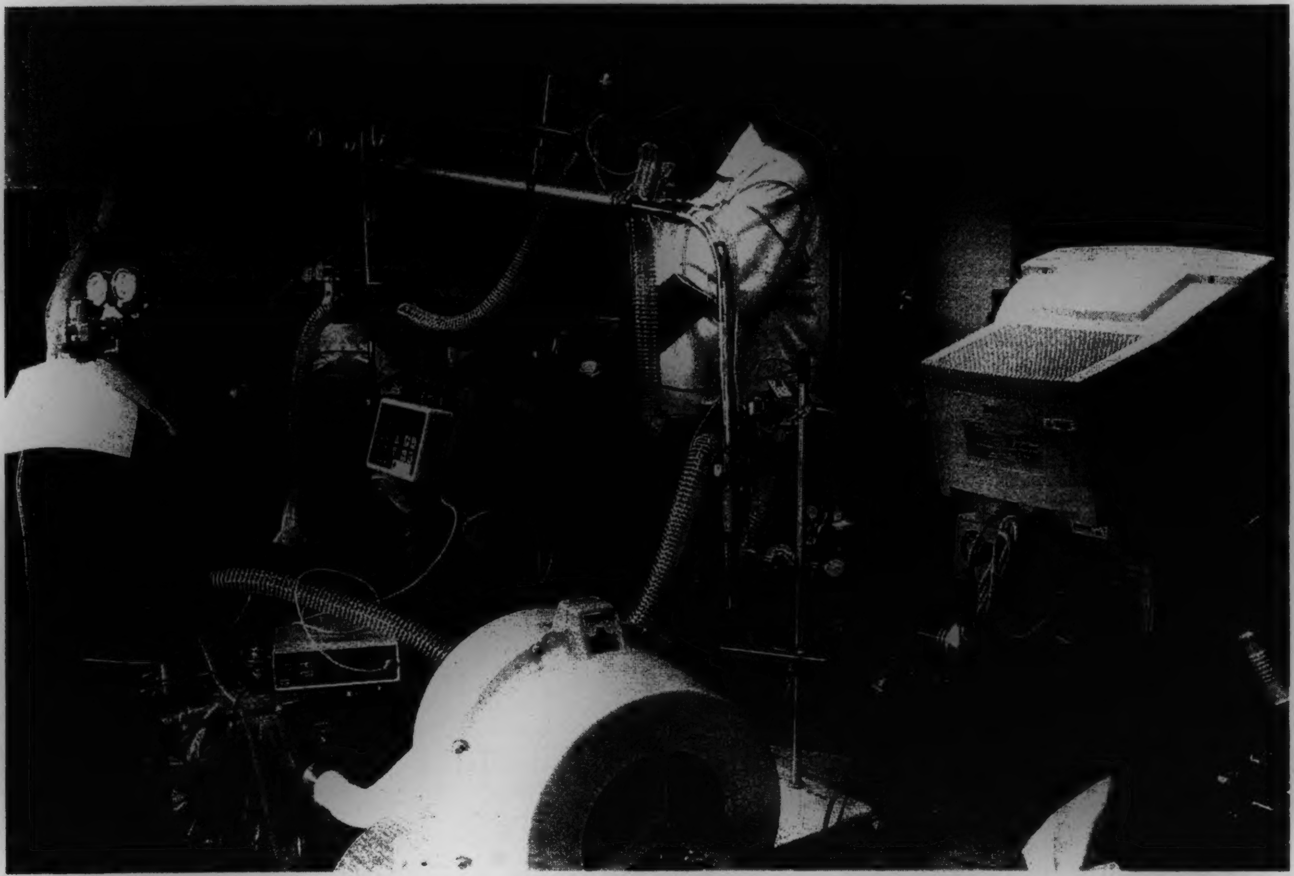


Figure A-7: The experimental set-up of the apparatus used during the exercise tolerance trials.

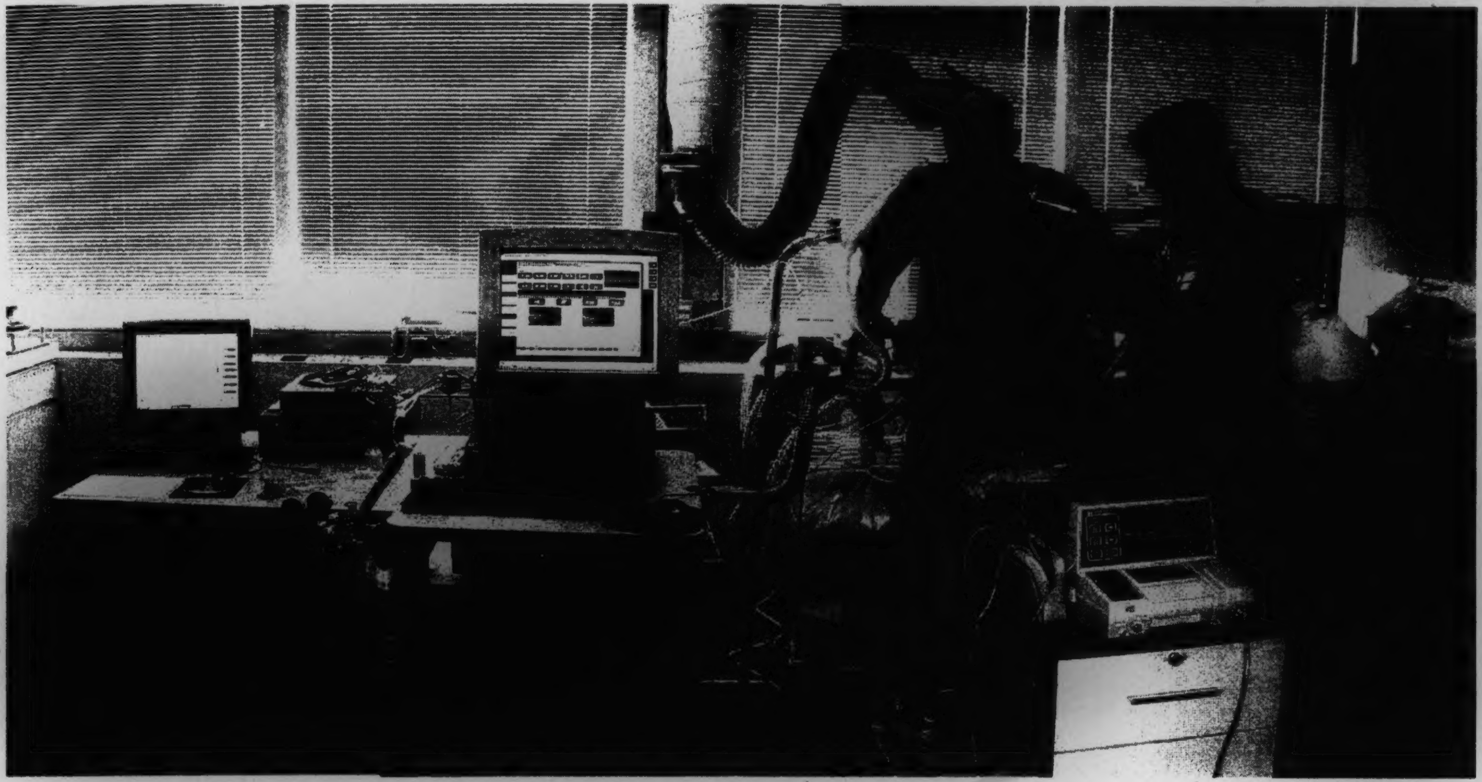


Figure A-8: The experimental set-up of the apparatus used during the exercise tolerance trials.

APPENDIX B

ADDITIONAL METHODOLOGY

Esophageal Balloon Insertion

Esophageal pressure was measured by an esophageal balloon (Ackrad Laboratories Inc., Cranford, NJ) placed ~ 45cm from the nostril. Subjects sat on a stool and the nostril and the back of the throat, were sprayed with local anesthetic (Xilocaine®, Lidocaine Hydrochloride 12 mg/metered dose). With the patient's head in a neutral or slightly forward flexed position the balloon tipped catheter, with 2% Xilocaine® anesthetic jelly applied to the end (Lidocaine Hydrochloride 20 mg/metered dose), was passed through the naris and hypopharynx and swallowed into the esophagus with the aid of sipping water through a straw. The catheter was advanced into the stomach (indicated by a positive pressure on inspiration) and then withdrawn approximately 10 cm and positioned in the lower third of the esophagus. Subjects were asked to perform a brief Valsalva maneuver while the catheter was open to the atmosphere to empty the balloon. Following this, 1.0 ml of air was administered into the balloon using a syringe as per the manufacturers recommendations. The validity of the balloon position was assessed using the "occlusion test" of Baydur et al., (1982). Once positioned, the catheter was secured using small pieces of tape that attached the catheter to the nostril. The balloon was also taped to the cheek to avoid catching it on the mouthpiece when performing the pulmonary function measures.

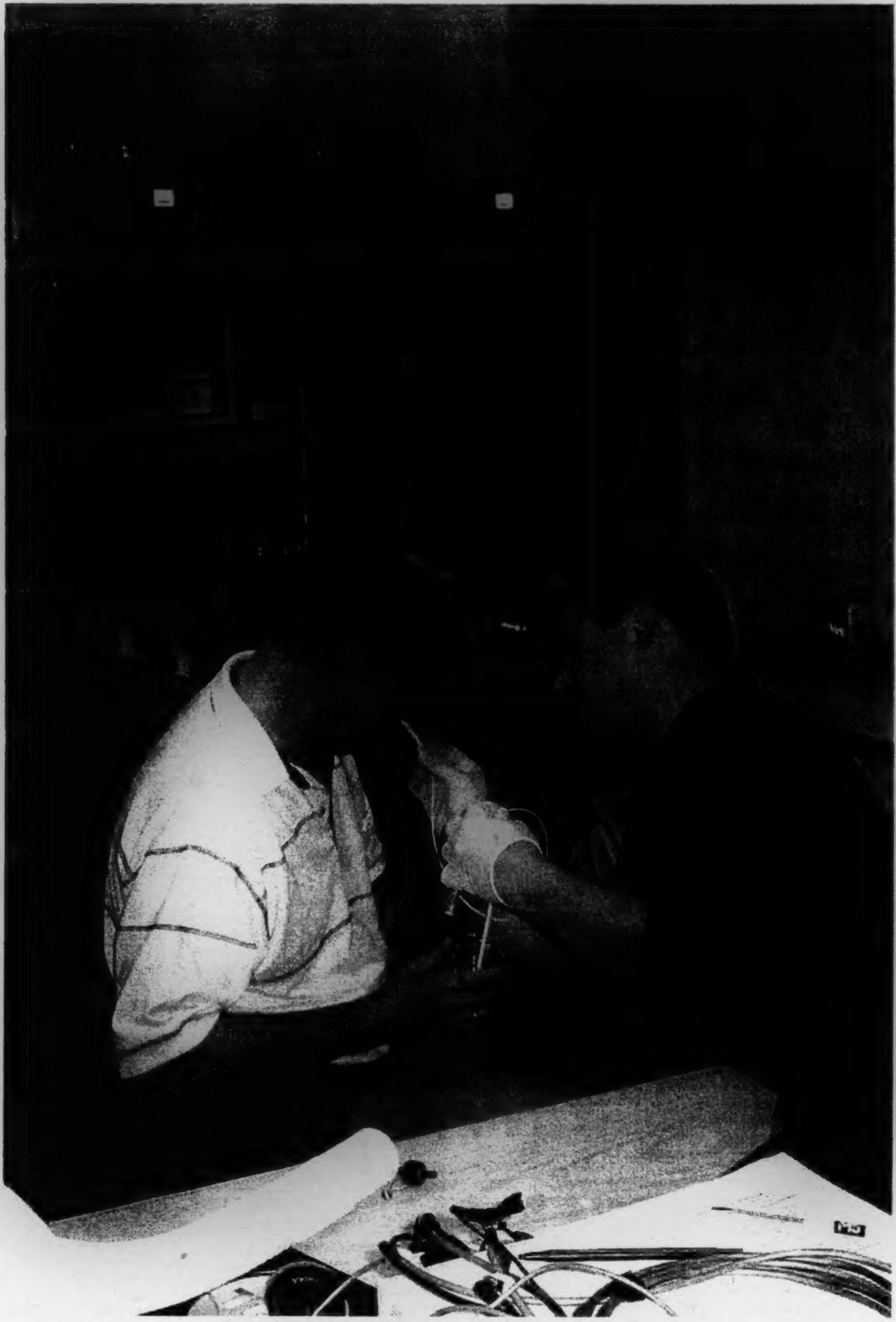


Figure B-1: Esophageal Balloon insertion used for the measurement of the work of breathing.

Calculating the Work of Breathing

The work of breathing was calculated using the technique of Yan et al., (1997) and Sliwinski et al., (1998) and is schematically depicted in Figure B-2. Assuming that chest wall compliance is normal in COPD (Sharp et al., 1968, Fleury et al., 1985) the static chest wall volume-pressure compliance of our participants was obtained from the literature (Estenne et al., 1983). This relationship was plotted and positioned as previously explained by Sliwinski et al., (1998). More specifically, the esophageal pressure at end expiration during quiet breathing was determined (Point F in Figure B-2) and the static chest wall compliance was started from this point. Clockwise esophageal pressure-volume loops during tidal breathing were then superimposed on the static chest wall pressure-volume compliance line.

End expiratory lung volume during exercise is represented in Figure B-2 by points E and A. Point E lies above point F indicating dynamic hyperinflation. Point E also represents the start of inspiratory effort, while point A is when inspiratory flow starts. Therefore, the difference between points E and A is the pressure needed to overcome PEEPi. Points A and B represent zero flow points at the start and end of inspiration, respectively, and the line that connects the two points is indicative of dynamic lung compliance. Therefore, the resistive work of breathing on inspiration is the area to the right of the dynamic pressure-volume tracing enclosed by the dynamic lung compliance line. The total elastic work performed on inspiration is the area enclosed by ABDEA. However, the different components of inspiratory work performed on inspiration can also be calculated by drawing a line, parallel to the static lung pressure-volume curve passing through point A (line A to C in Figure B-2). As a result, the work to overcome the elastic recoil of the lung or the "non-PEEPi" load (W_{INP}) is represented by the area ABCA and the remaining area (ACDEA) is the work to overcome PEEPi (W_{IP}). Finally, the additional respiratory muscle work performed by the respiratory muscles during expiration was also calculated as the area enclosed by the dynamic esophageal pressure-volume loop that lay to the right of the static chest wall compliance line.

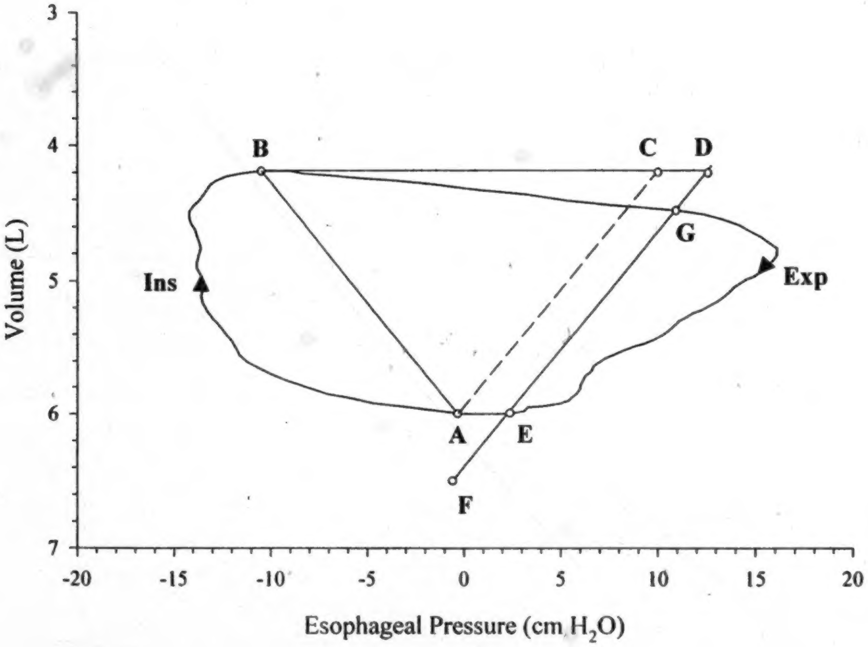


Figure B-2: Figure depicts the technique used for measuring the work of breathing. An esophageal pressure-volume loop during tidal breathing superimposed on the static chest wall pressure-volume compliance relationship (Line FED). Abbreviations and relevant areas are summarized below:
Ins = Inspiration. Exp = Expiration
A and E = End expiratory lung volume
A = Beginning of inspiratory flow (zero flow points)
B = End of inspiratory flow (zero flow points)
E - A = PEEPi
Total inspiratory work = area ABDEA
Resistive inspiratory work = area AInsBA
W_{IP} = area ACDEA
W_{INP} area ABCA
Active expiratory work = area EGE

APPENDIX C

ADDITIONAL RESULTS – STUDY THREE

Table C-1: Ventilatory Responses to Exercise

	AIR	HOX	HE-OX	HE-HOX
Rest				
V_E, Lmin^{-1}	17.3 ±3.9	16.7±3.4	15.9±5.8	15.5±4.4
V_T, L	1.16 ±0.47	1.10±0.31	1.17±0.37	1.15±0.48
f,	16.0 ±4.69	16.0±4.2	14.4±4.6	14.4±3.41
T_I	1.68 ± 0.57	1.69±0.50	1.90±0.59	1.87±0.65
T_E	2.35 ±0.61	2.29±0.74	2.58±0.54	2.51±0.45
T_I/T_{TOT}	0.42±0.07	0.43±0.11	0.42±0.05	0.42±0.08
V_E/VCO_2	55±7	56±5	55±12	51±8
V_E/VO_2	48±6	48±9	49±15	45±12
V_T/V_E	0.50±0.13	0.53±0.23	0.46±0.16	0.45±0.14
Isotime One				
V_E, Lmin^{-1}	$47.1\pm16.0^{b,d}$	$40.7\pm11.5^{a,c}$	$48.0\pm17.8^{b,d}$	$41.5\pm11.7^{a,c}$
V_T, L	$1.64\pm0.0.36^{c}$	1.67±0.40	1.82 ± 0.48^{a}	1.73±0.42
f,	$28.6\pm7.0^{b,d}$	24.5 ± 5.0^{a}	26.2±6.83	$24.1\pm^{a4.26}$
T_I	0.86 ± 0.26^{d}	0.99±0.20	0.95±0.25	1.06 ± 0.19^{a}
T_E	1.37 ± 0.35^{b}	1.56 ± 0.35^{a}	1.49±0.39	1.51±0.36
T_I/T_{TOT}	0.38±0.04	0.39±0.04	0.39±0.03	0.41±0.06
V_E/VCO_2	42 ± 7^{d}	38±8	40±4	36 ± 4^{a}
V_E/VO_2	$37\pm8^{b,d}$	$33\pm8^{a,c}$	36 ± 7^{b}	33 ± 6^{a}
V_T/V_E	1.28 ± 0.46^{b}	$1.12\pm0.36^{a,c}$	1.32 ± 0.56^{b}	1.21 ± 0.44^{b}
Isotime Two				
V_E, Lmin^{-1}	$52.7\pm22.4^{b,d}$	$43.5\pm12.6^{a,c}$	$54.0\pm20.7^{b,d}$	$44.4\pm13.7^{a,c}$
V_T, L	$1.69\pm0.55^{c,d}$	1.72 ± 0.55^{c}	$1.90\pm0.44^{a,b}$	1.85 ± 0.49^{a}
f,	$32.3\pm12.6^{b,d}$	25.9 ± 5.3^{a}	27.8±6.9	23.9 ± 3.81^{a}
T_I	0.85±0.42	0.91±0.86	0.84±0.20	1.02±0.15
T_E	1.27 ± 0.44^{d}	1.51±0.40	1.45±0.43	1.55 ± 0.31^{a}
T_I/T_{TOT}	0.39±0.04	0.38±0.03	0.37±0.02	0.40±0.04
V_E/VCO_2	40±7	35 ± 2^{c}	$44\pm6^{b,d}$	35 ± 2^{c}
V_E/VO_2	36±7	32 ± 5^{c}	$40\pm7^{b,d}$	33 ± 4^{c}
V_T/V_E	$1.45\pm0.61^{b,d}$	$1.18\pm0.39^{a,c}$	$1.44\pm^{b,d}$	$1.24\pm0.41^{a,c}$

Table C-1: Ventilatory Responses to Exercise (Continued)

Parameters	NOX	HOX	HE-OX	HE-HOX
Isotime Three				
V_E, Lmin^{-1}		50.3±19.1		49.3±16.7
V_T, L		1.74±0.62		1.85±0.61
f,		29.9±9.95		27.1±5.99
T_I		0.83±0.24		0.85±0.16
T_E		1.37±0.46		1.47±0.43
T_I/T_{TOT}		0.38±0.02		0.37±0.03
V_E/VCO_2		37±4		36±3
V_E/VO_2		34±6		32±6
V_T/V_E		1.36±0.56		1.32±0.48
End Exercise				
V_E, Lmin^{-1}	52.7±22.4^{C}	50.5±19.1^{c}	61.1±27.4^{a,b}	54.2±22.5
V_T, L	1.69±0.55^{c,d}	1.74±0.56^{c}	1.90±0.06^{a,b}	1.84±0.64^{a}
f,	32.3±12.6	29.8±9.8	32.1±10.6	29.7±7.8
T_I	0.85±0.42	0.83±0.25	0.68±0.22	0.76±0.18
T_E	1.27±0.44	1.36±0.40	1.35±0.41	1.40±0.46
T_I/T_{TOT}	0.39±0.04	0.38±0.02	0.34±0.06^{a}	0.36±0.03
V_E/VCO_2	40±7	37±4^{c}	42±6^{b}	39±5
V_E/VO_2	36±7	34±6^{c}	39±8^{b}	36±8
V_T/V_E	1.45±0.61	1.37±0.55	1.57±0.80	1.47±0.61

Abbreviations: V_E = Ventilation, V_T = tidal volume, f = breathing frequency, T_I = inspiratory time, T_E = expiratory time, T_I/T_{TOT} = ratio of inspiratory time to total time, V_E/VCO_2 = ventilatory equivalent for CO_2, V_E/VO_2 = ventilatory equivalent for O_2, V_T/V_E = expiratory flow rate. Values are means ± SD, n=11. For a explanation of the three isotimes please see text, a = $p<0.05$ vs. AIR, b = $p<0.05$ vs. HOX; c = $p<0.05$ vs. HE-OX; d = $p<0.05$ vs. HE-HOX